Hydroboration. 81. Synthesis of 2-(Dialkylamino)boronic Esters and Acids via Hydroboration of Enamines. A Convenient Preparation of β-Dialkylamino Alcohols

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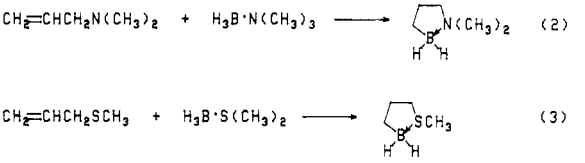
Hydroboration of representative enamines with 1 equiv of borane–dimethyl sulfide (BMS) in tetrahydrofuran affords as the major product the corresponding [2-(dialkylamino)alkyl]boranes, which are characterized by ^{11}B NMR spectroscopy. These intermediates on methanolysis give the corresponding [2-(dialkylamino)alkyl]boronates. On treatment with water, these esters undergo rapid hydrolysis to provide the 2-[(dialkylamino)alkyl]boronic acids in essentially quantitative yields. The boronic acids thus obtained can be reesterified with 1,3-propanediol to give the corresponding 2-[2-(dialkylamino)alkyl]-1,3,2-dioxaborinanes. Consequently, it is now possible to prepare dialkylamino-substituted organoborane compounds with the potential to be elaborated to a wide variety of functionalized trialkylamines. Alkaline hydrogen peroxide oxidation of these organoborane intermediates affords the corresponding β-dialkylamino alcohols. The hydroboration of enamines, methanolysis of the intermediate borane derivatives, and oxidation of the boronate esters is accompanied by side reactions such as elimination and protonolysis. The magnitude of these side reactions varies considerably with the structures of the enamines. However, moderate to excellent yields of the desired organoboron compounds can frequently be achieved. The use of trimethylamine *N*-oxide dihydrate for the oxidation of the 2-(dialkylamino) boronate esters greatly suppresses the side reactions and vastly improves the yields of the β-dialkylamino alcohols.

The remarkably facile reactions of olefins, acetylenes, and dienes with a variety of hydroborating agents have opened up a highly convenient route to a large variety of organoboranes.[2] The ability of the organoboranes to undergo a wide variety of chemical transformations has placed them among the most useful and versatile intermediates available to the organic chemist.[2] Perhaps one of the more intriguing features about hydroboration is the observation that many unsaturated molecules containing functional substituents are readily hydroborated and converted to the corresponding organoboranes.[3]

The hydroboration of 3-butenyl, 2-butenyl, and 1-butenyl derivatives containing representative substituents was studied systematically in our laboratories.[4] It was observed that such hydroborations can proceed with a remarkable regioselectivity, placing essentially all of the boron atom at the β-position. However, the organoboranes containing a heteroatom at the β-position were inclined to undergo 1,2-elimination, rendering relatively difficult the isolation of the organoborane intermediate (eq 1).[4-6]

Unlike the hydroboration of simple olefins, which generally proceeds rapidly past the monoalkylborane stage to the dialkylborane or the trialkylborane stage, the hydroboration of allylic amines and sulfides proceeds only to the monoalkylborane stage due to intramolecular complexation (eq 2 and 3).[7,8] Such intermediates can be readily hydrolyzed or methanolized to the corresponding boronic acids or esters, respectively. The single organic group in boronic acid derivatives can be quantitatively incorporated into organic molecules. Consequently, alkylboronic acids and esters are exceptionally promising intermediates for carbon–carbon bond-forming reactions.[9,10] Recently, we have converted a wide variety of boronic esters into aldehydes,[10] acids,[11] and primary amines.[12]



Since a number of organic amines are extremely important as therapeutic agents for the treatment of a variety of human disorders, we chose to investigate the hydroboration of enamines as a possible route to the [2-(dialkylamino)alkyl]boronic acid derivatives and amine-functionalized organic compounds. Although there have been several reports on the hydroboration of enamines leading to amino alcohols,[13] tertiary amines,[14] olefins,[15] and

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(2) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via* Boranes; Wiley-Interscience: New York, 1975.

(3) (a) Brown, H. C.; Sharp, R. L. *J. Am. Chem. Soc.* **1966**, *88*, 5851. (b) Klein, J.; Dunkelblum, E. *Tetrahedron Lett.* **1966**, 6047. (c) Pasto, D. J.; Miesel, J. L. *J. Am. Chem. Soc.* **1963**, *85*, 2118. (d) Nussim, M.; Mazur, Y.; Sondheimer, F. *J. Org. Chem.* **1964**, *29*, 1120. (e) Caglioti, L.; Cainelli, G.; Maina, G. *Tetrahedron* **1963**, *19*, 1057.

(4) (a) Brown, H. C.; Unni, M. K. *J. Am. Chem. Soc.* **1968**, *90*, 2902. (b) Brown, H. C.; Gallivan, R. M., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 2906. (c) Brown, H. C.; Sharp, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 2915. (d) Brown, H. C.; Knights, E. F. *J. Am. Chem. Soc.* **1968**, *90*, 4439.

(5) (a) Pasto, D. J.; Snyder, R. *J. Org. Chem.* **1966**, *31*, 2773. (b) Pasto, D. J.; Snyder, R. *J. Org. Chem.* **1966**, *31*, 2777. (c) Pasto, D. J.; Hickman, J. *J. Am. Chem. Soc.* **1968**, *90*, 4445. (d) Pasto, D. J.; Cumbo, C. C. *J. Am. Chem. Soc.* **1964**, *86*, 4343.

(6) Mikhailov, B. M.; Shchegoliva, T. A. *Izv. Akad. Nauk. SSSR* **1959**, 546.

(7) (a) Polivka, Z.; Ferles, M. *Collect. Czech. Chem. Commun.* **1969**, *34*, 3009. (b) Polivka, Z.; Kubelka, V.; Holubova, N.; Ferles, M. *Collect. Czech. Chem. Commun.* **1970**, *35*, 1131.

(8) Braun, R. A.; Brown, D. C.; Adams, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 2823.

(9) (a) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. *Organometallics* **1983**, *2*, 1536. (b) Matteson, D. S.; Sadu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077.

(10) Brown, H. C.; Imai, T. *J. Am. Chem. Soc.* **1983**, *105*, 6285.

(11) (a) Brown, H. C.; Imai, T.; Desai, M. C.; Singaram, B. *J. Am. Chem. Soc.* **1985**, *107*, 4980. (b) Brown, H. C.; Imai, T. *J. Org. Chem.* **1984**, *49*, 892.

(12) Brown, H. C.; Kim, K. W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761.

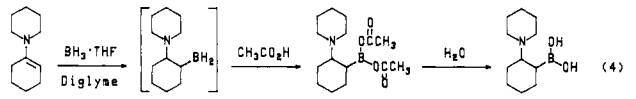
(13) (a) Borowitz, I. J.; Williams, G. J. *J. Org. Chem.* **1967**, *32*, 4157. (b) Mueller, R. H.; Thompson, M. E. *Tetrahedron Lett.* **1980**, *21*, 1093.

(14) (a) Marshall, J. A.; Johnson, W. S. *J. Org. Chem.* **1963**, *28*, 421. (b) Gore, J.; Barieux, J. J. *Tetrahedron Lett.* **1970**, 2849. (c) Barieux, J. J.; Gore, J. *Tetrahedron* **1972**, *28*, 1537, 1555.

0022-3263/87/1952-4014$01.50/0

1,2-carbonyl transposition,[16] a clear understanding of the optimum conditions required for clean and efficient hydroboration of enamines is truly lacking.

Additionally, preparation of the [2-(dialkylamino)alkyl]boronic acid derivatives from enamines is at the present time virtually unknown. A single example of such a preparation has been cited in the literature.[15a] Thus, in 1964, Lewis and Pearce reported that hydroboration of 1-piperidinocyclohexene with excess borane–tetrahydrofuran complex (BH_3·THF) in diglyme, followed by treatment of the intermediate organoborane with acetic acid and then water, gave an 85% yield of *trans*-(2-piperidinocyclohexyl)boronic acid (eq 4). Unfortunately,



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our efforts to repeat this synthesis were unsuccessful. It occurred to us that simple methanolysis of the intermediate monoalkylborane derivatives might provide a convenient route to the [2-(dialkylamino)alkyl]boronate esters, with subsequent hydrolysis affording the corresponding boronic acids. In this paper we report the preparation of 2-(dialkylamino)organoboranes and the conversion of these to the corresponding [2-(dialkylamino)alkyl]boronic esters and acids, often in excellent yields.

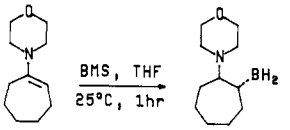
Results and Discussion

The following enamines were selected for this study: 1-pyrrolidinocyclopentene, 1-morpholinocyclopentene, 1-piperidinocyclohexene, 1-(benzylmethylamino)cyclohexene, 1-morpholinocyclohexene, 1-morpholinocycloheptene, 1-morpholinocyclooctene, and 1-morpholinocyclododecene. We also included one acyclic enamine, (*E*)-1-morpholino-1-phenyl-1-propene, in this study. The enamines were prepared by the method of Stork et al.[17] Although *p*-toluenesulfonic acid is a catalyst for this reaction and was used in a few of our reactions, we observed that some reactions were cleaner and the yields of enamines slightly greater when *p*-toluenesulfonic acid was not used. Three of the enamines, 1-pyrrolidinocyclopentene, 1-morpholinocyclopentene, and 1-morpholinocyclohexene, were commercial products.

Hydroboration. The hydroboration of 1-(dialkylamino)cycloalkenes with 1 equiv of borane–tetrahydrofuran gives the corresponding *trans*-2-(dialkylamino)-cycloalkylborane as the major product. Similar results were obtained when borane–dimethyl sulfide (BMS) was used as the hydroborating agent. Since BMS is easy to handle, we used this reagent routinely in this study. A standard procedure was generally followed: To an ice-cold tetrahydrofuran (THF) solution of the enamine was added 1 equiv of BMS. After the addition, the reaction was stirred for 1 h at 25 °C. An aliquot was then withdrawn and analyzed by ^{11}B NMR spectroscopy.

The organoborane intermediates obtained from 1-morpholinocyclopentene and 1-morpholinocyclohexene with 1 equiv of BMS gave complex ^{11}B NMR spectra, which yielded inconclusive structural information. However, the reaction of 1-morpholinocyclopentene with 2 equiv of BMS for 1 h at 25 °C followed by treatment with half an equivalent of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) led to the slow, quantitative precipitation of TMEDA·BH_3[18] over a period of 12 h. A similar experiment with 1-morpholinocyclohexene yielded no precipitate of TMEDA·BH_3. Apparently, *trans*-(2-morpholinocyclopentyl)borane forms a loose complex with the second equivalent of BH_3 and *trans*-(2-morpholinocyclohexyl)borane forms a very stable complex with the second equivalent of BH_3. Carrying out the hydroboration at 65 °C or using an excess of BMS resulted in the formation of complex reaction products due to extensive elimination followed by hydroboration of the olefin produced.

In contrast to the above results, the hydroboration of 7-, 8-, and 12-membered ring morpholine enamines very cleanly produces the corresponding monoalkylboranes, which exhibit a triplet at δ −2 to −3 in the ^{11}B NMR spectra (eq 5 and 6). It is convenient to refer to these mono-



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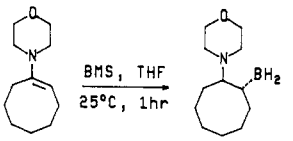

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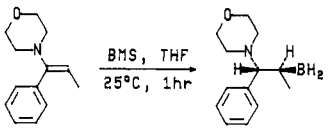
alkylboranes as simple borane derivatives. However, their ^{11}B NMR chemical shifts indicate that the BH_2 group is strongly coordinated to the morpholine moiety.

Similarly, the hydroboration of the acyclic enamine (*E*)-1-morpholino-1-phenyl-1-propene[19] with 1 equiv of BMS affords the corresponding monoalkylborane, which displays a triplet at δ −2.2 in the ^{11}B NMR spectrum (eq 7). Addition of a second equivalent of BMS to these



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well-defined monoalkylboranes caused no change in the ^{11}B NMR chemical shifts or the multiplicity of the signal, and a separate quartet at δ −20 for free BMS was observed. An excess of enamine also had no effect on the ^{11}B NMR characteristics of these monoalkylboranes.

A possible explanation for the difference in the behavior of the 5- and 6-membered ring enamines in the hydroboration stage as compared to that of the 7-, 8-, and 12-membered ring enamines, as well as the acyclic derivative, can be visualized in terms of the flexibility of the borane intermediate. In the case of the more flexible derivatives internal coordination can occur, similar to that shown in eq 2. These are apparently stable, so that the addition of BMS has no effect and the ^{11}B NMR spectra show two distinct species.

In the case of five- and six-membered ring enamines, the initial borane derivative can only coordinate with the trans tertiary amino nitrogen by forcing considerable distortion

(15) (a) Lewis, J. W.; Pearce, A. A. *Tetrahedron Lett.* **1964**, 2039. (b) Lewis, J. W.; Pearce, A. A. *J. Chem. Soc. B* **1969**, 863. (c) Friary, R. J.; Gilligan, J. M.; Szajewski, R. P.; Fulci, K. J.; Franck, R. W. *J. Org. Chem.* **1973**, *38*, 3487. (d) Froberg, J.; Magnusson, G.; Thoren, S. *Tetrahedron Lett.* **1975**, 1621. (e) Montury, M.; Gore, J. *Tetrahedron Lett.* **1977**, 219. (f) Froberg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728.

(16) (a) Gore, J.; Drouet, J. P.; Barieux, J. J. *Tetrahedron Lett.* **1969**, 9. (b) Barieux, J. J.; Gore, J. *Bull. Soc. Chim. Fr.* **1971**, 1649, 3978.

(17) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(18) Brown, H. C.; Singaram, B. *Inorg. Chem.* **1980**, *19*, 455.

(19) This compound was demonstrated to have the *E* geometry by two-dimensional NMR techniques. The details of this study will be presented in a forthcoming separate publication. Hasha, D. Analytical Laboratory, Michigan Applied Science and Technology Laboratories, The Dow Chemical Company, Midland, MI 48674. Private communication.

Table I. [2-(Dialkylamino)alkyl]boranes

monoalkylboranes RBH_2, R =	yield,[a] %	mp,[b] °C	^{11}B NMR chem shift δ[c] (mult)	^{11}B NMR J_{BH}, Hz
trans-2-morpholinocycloheptyl	>95	44–48	−1.9 (t)	105
trans-2-morpholinocyclooctyl	>95	50–54	−2.7 (t)	106
trans-2-morpholinocyclododecyl	>95	*d*	−2.9	*e*
threo-1-morpholino-1-phenyl-2-propyl	>95	*d*	−2.2 (t)	105

[a] Isolated yield of the crude monoalkylborane. [b] Melting points are uncorrected and were obtained in sealed capillary tubes. [c] Relative to $EE{\cdot}BF_3$ (δ 0). [d] Viscous liquid at 25 °C. [e] Unresolved triplet.

Table II. [2-(Dialkylamino)alkyl]boronic Esters and Acids

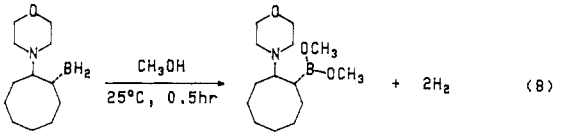
	boronic esters, $RB(OR')_2$[a]			boronic acids, $RB(OH)_2$	
R	yield,[b] %	bp, °C (Torr)	^{11}B NMR chem shift δ[c]	yield,[b] %	mp,[d] °C
trans-2-morpholinocyclopentyl	40	98–100 (0.5)	+32		
trans-2-(benzylmethylamino)cyclohexyl	50	120–122 (0.6)	+31		
trans-2-morpholinocyclohexyl	68	118–120 (0.6)	+31	85	114–116
trans-2-morpholinocyclohexyl[e]	60	120–122 (0.5)	+30		
trans-2-piperidinocyclohexyl[e]	40	108–110 (0.2)	+29		
trans-2-morpholinocycloheptyl	73	110–112 (0.6)	+30	90	100–102
trans-2-morpholinocyclooctyl	75	128–130 (1.0)	+29	90	102–104
trans-2-morpholinocyclododecyl[f]	86	78–80[g]	+30	84	106–108
threo-1-morpholino-1-phenyl-2-propyl	80	116–118 (0.3)	+31	90	108–110

[a] Dimethyl esters unless otherwise stated. [b] Isolated yield. [c] Relative to $EE{\cdot}BF_3$ (δ 0). [d] Melting points are uncorrected and were obtained in sealed capillary tubes. [e] 1,3-Propanediol esters obtained from the hydroboration product. [f] 1,3-Propanediol ester obtained from the corresponding boronic acid. [g] Melting point.

on the system. In these cases the additional mole of BMS results in a competitive coordination with the tertiary amino group and one sees evidence for an equilibration between BMS and the borane adduct of the initial product.

Methanolysis to Boronic Esters. The clean formation of simple borane derivatives from the 7-, 8-, and 12-membered ring enamines led us to explore simple reactions to transform the RBH_2 group. One route we explored was the possibility that these [2-(dialkylamino)alkyl]boranes might hydroborate simple terminal olefins such as 1-hexene. However, treatment of *trans*-(2-morpholinocyclooctyl)borane with 2 equiv of 1-hexene in THF at 25 °C gave no reaction even after 24 h.

Even though the B–H bonds in the 7-, 8-, and 12-membered ring monoalkylboranes are virtually inert toward further hydroboration, they react very rapidly with methanol to afford the corresponding dimethyl *trans*-[2-(dialkylamino)cycloalkyl]boronates in excellent yield (eq 8). In contrast, the organoborane intermediates obtained



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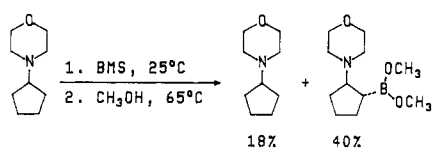
from the five- and six-membered ring enamines reacted more slowly with methanol. The methanolysis was complete in 12 h, however, and gave the corresponding dimethyl boronate esters as the major product. Alternatively, the methanolysis at 65 °C was complete in 3 h. However, under these reaction conditions the organoborane intermediates obtained from the five-membered ring enamines afforded varying amounts of protonolyzed products along with the desired dimethyl esters (eq 9).



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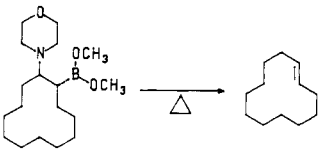
The protonolyzed product apparently arises during the methanolysis, since treating the hydroboration product from 1-pyrrolidinocyclopentene with CH_3OD gave 1-cyclopentylpyrrolidine containing 1 to 4 deuterium atoms in the carbocyclic ring as determined by EI/GC/MS and two-dimensional ^{13}C NMR techniques.[20,21]

In all cases, except one, the dimethyl [2-(dialkylamino)alkyl]boronate esters were easily purified by vacuum distillation (Table II). The exception, dimethyl (*trans*-2-morpholinocyclododecyl)boronate, decomposed upon attempted distillation, giving *trans*-cyclododecene (eq 10).[22]



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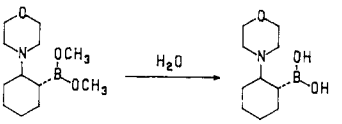
The dimethyl boronate esters were readily hydrolyzed with water to give the corresponding boronic acids (eq 11, Table II). Alternatively, the crude dimethyl boronate



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esters were extracted with *n*-pentane and the *n*-pentane extracts upon aqueous hydrolysis furnished the boronic acids.

The boronic acids can be reesterified with 1,3-propanediol in *n*-pentane to give the corresponding cyclic boronate esters.[23] The hydrolysis and reesterification with

(20) Zakett, D.; Hasha, D. Analytical Laboratory, Michigan Applied Science and Technology Laboratories, The Dow Chemical Company, Midland, MI 48674. Private communication. The details of the EI/GC/MS and two-dimensional NMR studies on the deuteriated 1-cyclopentylpyrrolidine will be presented in a forthcoming separate publication.

(21) A good explanation for the observed polydeuteriation is not forthcoming at this time.

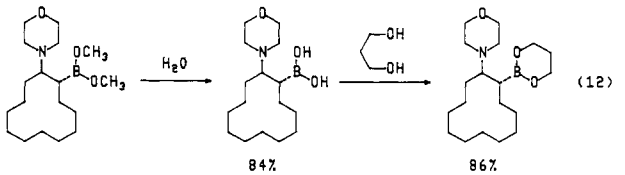
(22) The ^{13}C NMR spectrum of this material indicated that it was one isomer, and the spectrum agreed with that reported for *trans*-cyclododecene.

Table III. Conversion of Enamines into β-Dialkylamino Alcohols by Hydroboration-Oxidation[a]

enamine	β-dialkylamino alcohol[b]	isolated yield, %	bp, °C (Torr)
1-pyrrolidinocyclopentene	*trans*-2-pyrrolidinocyclopentanol[c]	54	100–104 (1.2)[i]
1-morpholinocyclopentene	*trans*-2-morpholinocyclopentanol[c]	53	110–114 (0.6)
1-piperidinocyclohexene	*trans*-2-piperidinocyclohexanol	76	88–90 (0.4)
1-morpholinocyclohexene	*trans*-2-morpholinocyclohexanol	92	90–92 (0.3)[j]
1-(benzylmethylamino)cyclohexene	*trans*-2-(benzylmethylamino)cyclohexanol	82	118–121 (0.3)
1-morpholinocycloheptene	*trans*-2-morpholinocycloheptanol[c]	66	98–100 (0.25)
1-morpholinocyclooctene	*trans*-2-morpholinocyclooctanol[c,d]	56	110–112 (0.2)
1-morpholinocyclododecene	*trans*-2-morpholinocyclododecanol[e,f]	27	144–148 (0.2)
(*E*)-1-morpholino-1-phenyl-1-propene	*threo*-1-morpholino-1-phenyl-2-propanol[e,g]	35 (70)[h]	86–88[k]

[a] Hydroboration was carried out by using 1 equiv of BMS in THF at 25 °C for 1 h. See Experimental Section. [b] Exhibited infrared spectra identical with that obtained from β-dialkylamino alcohols prepared from the corresponding secondary amines and the cycloalkene oxides. [c] Corresponding protonolyzed product was obtained as a byproduct. [d] Authentic β-dialkylamino alcohol could not be prepared from morpholine and cyclooctene oxide. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.78; N, 6.57. Found: C, 67.24; H, 11.53; N, 6.94. [e] Corresponding olefin was obtaind as the major product. [f] Anal. Calcd for $C_{16}H_{31}NO_2$: C, 71.32; H, 11.60; N, 5.20. Found: C, 71.62; H, 11.86; N, 5.48. [g] Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.39; H, 8.70; N, 6.20. [h] Isolated yield of the amino alcohol when trimethylamine *N*-oxide dihydrate was used as the oxidizing agent. [i] Lit. bp 78–80 °C (2 Torr). See ref 16b. [j] Lit. bp 95–95.5 °C (0.5 Torr). See ref 13a. [k] Melting point.

1,3-propanediol were used to determine the yield of dimethyl *trans*-(2-morpholinocyclododecyl)boronate, which could not be distilled (vide supra) but could be converted in high yield to the easily isolated, crystalline 1,3-propanediol ester (eq 12). Reaction of the initial hydroboration product of the enamines with 1,3-propanediol, followed by *n*-pentane extraction and distillation, also gave the corresponding cyclic boronate esters.



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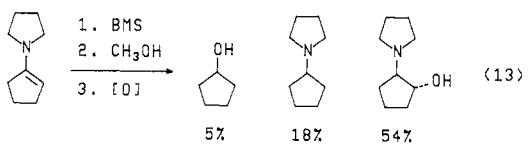
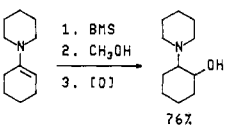
Oxidation to Amino Alcohols. As a proof of structure, the boronic acid derivatives were oxidized by using alkaline hydrogen peroxide to give the corresponding amino alcohols (Table III). However, we observed that the byproduct boric acid formed an addition compound with the amino alcohol, rendering purification of these compounds by distillation difficult. Treatment of the crude amino alcohol with methanolic hydrochloric acid gave methyl borate and the hydrochloride salt of the amino alcohol. The volatile methyl borate was readily removed under reduced pressure (25 °C, 12 Torr). The hydrochloride salt was treated with sodium hydroxide and the pure amino alcohol recovered by distillation. In most cases, the authentic *trans*-2-(dialkylamino)cycloalkanols could also be obtained by the reaction of the corresponding cycloalkene oxide with the appropriate dialkylamine.[24]

The yield of the amino alcohols produced and the side reactions, protonolysis and elimination, varied with the size of the carbocyclic ring of the starting enamine. Thus, the hydroboration, methanolysis, and alkaline hydrogen peroxide oxidation of 1-pyrrolidinocyclopentene gave a mixture of cyclopentanol, 1-cyclopentylpyrrolidine, and *trans*-2-pyrrolidinocyclopentanol (eq 13). The cyclopentanol presumably arises from an elimination of the borane derivative to give cyclopentene, followed by hydroboration and subsequent oxidation. The 1-cyclopentylpyrrolidine, the "reduction" product, presumably arises from protonolysis of the boron–carbon bond of the borane intermediate (vide supra). Finally, the amino alcohol is the anticipated product for the hydroboration, methanolysis to the dimethyl boronate ester, and the usual oxidation of the boron–carbon bond. Similar results were obtained for the hydroboration–oxidation of 1-morpholinocyclopentene.

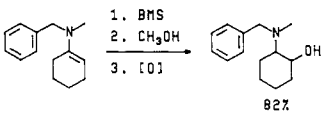


(13)

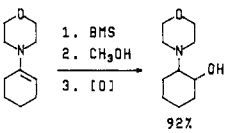
The 1-(dialkylamino)cyclohexenes gave the best yields of the corresponding amino alcohols with only minor amounts of the protonolysis products (eq 14–16).



(14)



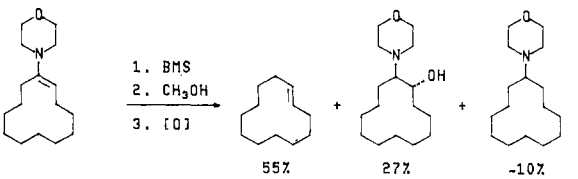
(15)



(16)

The hydroboration, methanolysis, and alkaline hydrogen peroxide oxidation of seven- and eight-membered ring morpholine enamines also afforded the corresponding *trans*-2-morpholinocycloalkanols. In these systems, the formation of protonolysis products was also observed.

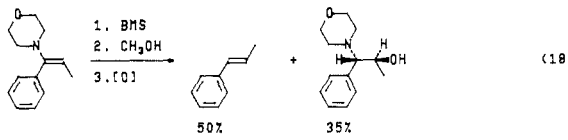
Elimination. In contrast to the above results, the hydroboration–oxidation of 1-morpholinocyclododecene afforded *trans*-cyclododecene as the major product. The corresponding amino alcohol and 4-cyclododecylmorpholine were obtained as the byproducts (eq 17).



(17)

Similarly, the acyclic enamine (*E*)-1-morpholino-1-phenyl-1-propene, upon hydroboration–oxidation, gave pure *trans*-β-methylstyrene in 50% yield and *threo*-1-morpholino-1-phenyl-2-propanol in 35% yield (eq 18). We made no effort to explore conditions that would favor this

(23) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311.
(24) Mousseron, M.; Jullien, J.; Jolchin, Y. *Bull. Soc. Chim. Fr.* **1952**, *19*, 757.



(18)

elimination reaction. However, the use of trimethylamine *N*-oxide dihydrate[25] as the oxidizing agent suppressed the elimination reaction to 5% and gave *threo*-1-morpholino-1-phenyl-2-propanol in 70% isolated yield.

It should be noted that our early studies of the hydroboration of crotyl derivatives revealed that elimination is strongly favored in systems in which the boron atom is β to a donor group. In the case of strong leaving groups such as halogen, the elimination is preferably trans.[3b] In the case of weak leaving groups, such as OR (and presumably NR_2), the elimination is cis, probably involving a cis coordination of boron with the donor atom of the substituent.[3d] The more flexible cyclododecyl and acyclic enamine systems can more readily achieve this cis coordination, thus accounting for the greater tendency of these systems to undergo elimination.

Conclusion

The present study demonstrates that enamines react rapidly with 1 equiv of borane–dimethyl sulfide complex (BMS) to give the corresponding [2-(dialkylamino)alkyl]boranes. The monoalkylboranes can be converted to the corresponding dimethyl [2-(dialkylamino)alkyl]boronates in moderate to excellent yields. These esters can then be hydrolyzed to the corresponding [2-(dialkylamino)alkyl]boronic acids. The monoalkylboranes obtained from enamines upon methanolysis and oxidation with alkaline hydrogen peroxide give good to excellent yields of the corresponding β-dialkylamino alcohols. The yields of the amino alcohols vary with the structure of the starting enamines, and in cyclic systems the best yields were obtained with 1-(dialkylamino)cyclohexenes. The relative importance of side reactions such as protonolysis and elimination also varies strongly with the structure of the starting enamine.

Experimental Section

All operations were carried out under a nitrogen atmosphere with oven-dried glassware.[2] The spectra were obtained in an inert atmosphere. The ^{11}B NMR spectra were recorded on a Varian FT-80A spectrometer and the chemical shifts are in δ relative to EE·BF_3 with chemical shifts downfield from EE·BF_3 assigned as positive. The ^1H NMR spectra were scanned on a Varian T-60 spectrometer. Gas chromatograph analyses were carried out with a Hewlett-Packard 5750 chromatograph using a 6 ft × 0.25 in. column packed with 10% Carbowax 20M on Chromasorb W (60–80 mesh).

Materials. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl prior to use. Anhydrous diethyl ether (EE) was purchased from Mallinckrodt, Inc., and was used directly. Borane–dimethyl sulfide (BMS, 10.0 M), 1-pyrrolidinylcyclopentene, 1-morpholinocyclopentene, and 1-morpholinocyclohexene were purchased from the Aldrich Chemical Company. Other enamines used in this study were prepared by literature methods.[17] *N,N,N',N'*-Tetramethylenediamine (TMEDA) was distilled from calcium hydride.

Hydroboration of 1-Morpholinocyclopentene with Two Equivalents of BMS. Analysis for Free Borane. A previously dried and nitrogen-flushed 50-mL centrifuge tube with a magnetic stirring bar was charged with 1-morpholinocyclopentene (1.54 g, 10 mmol) and THF (6.5 mL). The resulting solution was cooled to 0 °C and BMS (2.0 mL, 20 mmol) was slowly added. The reaction was stirred at 0 °C for 0.25 h and then at 25 °C for 1 h. An aliquot was withdrawn and analyzed by ^{11}B NMR spectroscopy. The proton-decoupled spectrum displayed signals at δ −10.8, −14.5, and −20.0. The proton-coupled spectrum showed that the peak at δ −20.0 was a quartet attributable to free BMS. The sample was returned to the reaction and TMEDA (0.75 mL, 5 mmol) was added. After a few minutes crystals slowly began to form and the reaction mixture was stirred at 25 °C for 12 h. The proton-decoupled ^{11}B NMR spectrum of the supernatant solution displayed a broad singlet at δ +0.1 and a sharp singlet at δ −9.5. The solid was washed and centrifuged three times with EE and dried under reduced pressure to give TMEDA·$2BH_3$ (0.74 g, 5.1 mmol), mp 182–184 °C.[18]

***trans*-(2-Morpholinocycloheptyl)borane.** The following procedure for the preparation of monoalkylborane from 1-morpholinocycloheptene is typical. A 100-mL flask equipped with a magnetic stirrer and a rubber septum was charged with 1-morpholinocycloheptene (3.61 g, 20 mmol) and THF (14.4 mL). The resulting solution was cooled to 0 °C and BMS (2.0 mL, 20 mmol) was slowly added. The reaction was then stirred at 25 °C for 1 h. The ^{11}B NMR spectrum of an aliquot displayed a triplet centered at δ −1.9 (J_{BH} = 105 Hz) characteristic of a monoalkylborane complexed with an amine nitrogen. The sample was returned to the reaction mixture. An aliquot (1.0 mL) of the reaction mixture was mixed with BMS (0.1 mL, 1 mmol) and the ^{11}B NMR spectrum now displayed a triplet at δ −1.9 for the monoalkylborane and a quartet at δ −20.0 for the free BMS. A second aliquot (1.0 mL) of the reaction mixture was taken and the solvents were removed under reduced pressure, leaving 0.213 g of the monoalkylborane as a white, crystalline solid, mp 44–48 °C (Table I).

Attempted Hydroboration of 1-Hexene with *trans*-(2-Morpholinocyclooctyl)borane. A 20-mL flask was charged with a solution of *trans*-(2-morpholinocyclooctyl)borane (5 mL, 5 mmol). To this solution was added 1-hexene (1.50 mL, 12 mmol). After stirring for 2 h at 25 °C, the reaction was analyzed by ^{11}B NMR. The spectrum displayed only the triplet at δ −2.7 for the monoalkylborane. The reaction was then refluxed for 24 h and again analyzed by ^{11}B NMR. The predominant peak in the spectrum was the triplet due to the monoalkylborane. A new, broad peak at δ +88 indicated that a small amount of reaction may have taken place. Thus, under the above conditions, the *trans*-(2-morpholinocyclooctyl)borane does not readily react with even simple, terminal olefins.

Preparation of Dimethyl *trans*-(2-Morpholinocyclohexyl)boronate. A 100-mL flask equipped with a magnetic stirrer and a rubber septum was charged with 1-morpholinocyclohexene (3.35 g, 20 mmol) and THF (14.4 mL). The resulting solution was cooled to 0 °C and BMS (2.0 mL, 20 mmol) was slowly added with stirring. The reaction was stirred at 25 °C for 1 h. Methanol (2.0 mL) was then added slowly to control the vigorous hydrogen evolution. The reaction mixture was stirred at 25 °C for 12 h to ensure complete methanolysis. The solvent and the volatiles were evaporated under reduced pressure (25 °C, 12 Torr). The crude boronate ester thus obtained was distilled under reduced pressure to give dimethyl *trans*-(2-morpholinocyclohexyl)boronate as a colorless liquid: 3.28 g (68%), bp 118–120 °C (0.06 Torr); ^{11}B NMR δ +31 (s); ^1H NMR ($CDCl_3$) δ 1.0–2.1 (m, 10 H), 2.2–2.9 (m, 4 H), 3.5 (s, 6 H), 3.4–3.8 (m, 4H).

Other dimethyl boronate esters were similarly prepared and the results are summarized in Table II.

Dimethyl *trans*-(2-morpholinocyclopentyl)boronate: ^1H NMR ($CDCl_3$) δ 1.2–2.0 (m, 8 H), 2.2–2.9 (m, 4 H), 3.6 (s, 6 H), 3.4–3.8 (m, 4 H).

Dimethyl *trans*-[2-(benzylmethylamino)cyclohexyl]boronate: ^1H NMR ($CDCl_3$) δ 1.0–1.92 (m, 10 H), 2.1 (s, 3 H), 3.6 (s, 6 H), 4.1 (s, 2 H), 7.2 (s, 5 H).

Dimethyl *trans*-(2-morpholinocycloheptyl)boronate: ^1H NMR ($CDCl_3$) δ 1.1–1.89 (m, 12 H), 2.1–2.8 (m, 4 H), 3.5 (s, 6 H), 3.4–3.8 (m, 4 H).

Dimethyl *trans*-(2-morpholinocyclooctyl)boronate: ^1H NMR ($CDCl_3$) δ 1.55 (br s, 14 H), 2.1–2.8 (m, 4 H), 3.6 (s, 6 H), 3.4–3.8 (m, 4 H).

Dimethyl *threo*-(1-morpholino-1-phenyl-2-propyl)boronate: ^1H NMR ($CDCl_3$) δ 0.7 (d, J = 7 Hz, 3 H), 1.4–2.9 (m, 5 H), 3.6 (s, 6 H), 3.4–3.8 (m, 4 H), 7.2 (br s, 5 H).

(25) Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Org. Chem.* **1975**, *40*, 1776.

Preparation of *threo*-(1-Morpholino-1-phenyl-2-propyl)-boronic Acid. The following procedure is representative. A 100-mL flask equipped with a magnetic stirrer and a rubber septum was charged with dimethyl *threo*-(1-morpholino-1-phenyl-2-propyl)boronate (2.77 g, 10 mmol) and *n*-pentane (17 mL). The resulting solution was reacted with water (0.4 mL) with stirring. The reaction mixture was stirred at 25 °C for 1 h. The boronic acid crystals thus formed were quickly separated by filtration, washed with *n*-pentane (5 mL), and dried under reduced pressure (25 °C, 12 Torr): 2.2 g (88%), mp 108–110 °C (Table II).

Alternatively, the crude dimethyl boronate esters were extracted with *n*-pentane and the *n*-pentane extracts upon aqueous hydrolysis furnished the corresponding boronic acid.

Synthesis of *trans*-2-(2-Morpholinocyclododecyl)-1,3,2-dioxaborinane. The following procedure is typical. *trans*-(2-Morpholinocyclododecyl)boronic acid (6.3 g, 20 mmol) was stirred with *n*-pentane (100 mL) and 1,3-propanediol (2.2 g, 30 mmol) at 25 °C. The boronic acid gradually dissolved (1.0 h) and water separated.[23] The reaction mixture was transferred to a separatory funnel. The reaction mixture was shaken for a few minutes and then the lower water layer that separated was removed. The *n*-pentene layer was dried over anhydrous magnesium sulfate, and upon removal of the solvent essentially pure ester was obtained: 5.8 g (86%), mp 78–80 °C; ^{11}B NMR δ +30 (s); ^{1}H NMR ($CDCl_3$) δ 1.37 (br s, 22 H), 1.8–2.1 (m, 2 H), 2.2–2.8 (m, 4 H), 3.6 (t, J = 4 Hz, 4 H), 3.97 (t, J = 7 Hz, 4 H).

Reaction of the initial hydroboration products with 1,3-propanediol followed by *n*-pentane extraction and distillation also gives the corresponding cyclic boronate esters (Table II).

***trans*-(2-Morpholinocyclohexyl)-1,3,2-dioxaborinane**: ^{1}H NMR ($CDCl_3$) δ 0.6–2.9 (m, 16 H), 3.6 (t, J = 4 Hz, 4 H), 3.95 (t, J = 7 Hz, 4 H).

***trans*-2-(2-Piperidinocyclohexyl)-1,3,2-dioxaborinane**: ^{1}H NMR ($CDCl_3$) δ 0.6–2.0 (m, 18 H), 2.1–2.95 (m, 4 H), 3.93 (t, J = 7 Hz, 4 H).

Preparation of *trans*-2-Morpholinocyclohexanol. The following procedure for the synthesis of *trans*-2-morpholinocyclohexanol from 1-morpholinocyhclohexene is representative. A 250-mL flask equipped with a magnetic stirrer and a rubber septum was charged with 1-morpholinocyclohexene (8.4 g, 50 mmol) and THF (37 mL). The solution was cooled to 0 °C and BMS (50 mL, 50 mmol) was slowly added with stirring. The reaction was stirred at 25 °C for 1 h and treated with methanol (8 mL, 200 mmol), and the stirring was continued for 12 h at 25 °C. The solvent and the volatiles were removed under reduced pressure (25 °C, 12 Torr) and the residue was dissolved in THF (37 mL) and methanol (8 mL). To this solution was added solid sodium hydroxide (2.8 g, 70 mmol) followed by the slow addition of 30% hydrogen peroxide (8 mL, 70 mmol). After the addition was complete, the reaction was stirred at 25 °C for 1 h and filtered. The reaction flask was washed with THF (3 × 10 mL) and filtered. The solvent was evaporated from the combined filtrate and the residue was dissolved in methanol (10 mL). The solution was acidified with concentrated hydrochloric acid (5 mL) and stirred at 25 °C for 0.25 h. The methanol and methyl borate were then removed under reduced pressure (25 °C, 12 Torr) and the residue was made basic with aqueous sodium hydroxide (10 mL, 60 mmol). It was then extracted with EE (4 × 25 mL) and the combined extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded the crude amino alcohol: 8.8 g (95%). GC analysis of the crude amino alcohol displayed a single peak. The amino alcohol was purified by distillation to give *trans*-2-morpholinocyclohexanol: 8.5 g (92%), bp 90–92 °C (0.3 Torr). The infrared spectrum (neat) of this material was identical with that of *trans*-2-morpholinocyclohexanol prepared from morpholine and cyclohexene oxide.

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Registry No. BMS, 13292-87-0; *trans*-2-morpholinocycloheptylborane, 109433-56-9; *trans*-2-morpholinocyclooctylborane, 109433-57-0; *trans*-2-morpholinocyclododecylborane, 109433-58-1; *threo*-1-morpholino-1-phenyl-2-propylborane, 109433-59-2; 1-morpholinocycloheptene, 7182-08-3; 1-morpholinocyclooctene, 17344-01-3; 1-morpholinocyclododecene, 3725-39-1; 1-morpholino-1-phenyl-2-propene, 30085-70-2; 1-pyrrolidinocyclopentene, 7148-07-4; 1-morpholinocyclopentene, 936-52-7; 1-piperidinocyclohexene, 2981-10-4; 1-morpholinocyclohexene, 670-80-4; 1-(benzylmethylamino)cyclohexene, 61581-04-2; 1-hexene, 592-41-6; dimethyl *trans*-2-morpholinocyclopentylboronate, 109433-60-5; dimethyl *trans*-2-(benzylmethylamino)-cyclohexylboronate, 109433-61-6; dimethyl *trans*-2-morpholinocyclohexylboronate, 109433-62-7; *trans*-2-morpholinocyclohexylboronic acid 1,3-propanediol ester, 109494-79-3; *trans*-2-piperidinocyclohexylboronic acid 1,3-propanediol ester, 109433-63-8; dimethyl *trans*-2-morpholinocycloheptylboronate, 109433-64-9; dimethyl *trans*-2-morpholinocyclooctylboronate, 109466-70-8; *trans*-2-morpholinocyclododecylboronic acid 1,3-propanediol ester, 109433-65-0; dimethyl *threo*-1-morpholino-1-phenyl-2-propylboronate, 109433-66-1; *threo*-1-morpholino-1-phenyl-2-propylboronic acid, 109433-67-2; *trans*-2-morpholinocyclohexylboronic acid, 109433-68-3; *trans*-2-morpholinocycloheptylboronic acid, 109433-69-4; *trans*-2-morpholinocyclooctylboronic acid, 109433-70-7; *trans*-2-morpholinocyclododecylboronic acid, 109433-71-8; 1,3-propanediol, 504-63-2; *trans*-2-pyrrolidinocyclopentanol, 32635-39-5; *trans*-2-morpholinocyclopentanol, 109433-72-9; *trans*-2-piperidinocyclohexanol, 7581-94-4; *trans*-2-morpholinocyclohexanol, 14909-79-6; *trans*-2-(benzylmethylamino)cyclohexanol, 109433-73-0; *trans*-2-morpholinocycloheptanol, 109433-74-1; *trans*-2-morpholinocyclooctanol, 109433-75-2; *trans*-2-morpholinocyclododecanol, 109433-76-3; *threo*-1-morpholino-1-phenyl-2-propanol, 109433-77-4.