19: NMR ($CDCl_3$) δ 2.27-2.37 (m, 2 H), 2.70-2.77 (m, 2 H), 3.16-3.22 (m, 2 H), 3.62 (q, J_{AB} = 9, 17 Hz, 1 H), 4.12-4.26 (m, 2 H), 6.50 (d, J = 6 Hz, 1 H), 6.87 (d, J = 9 Hz, 1 H), 7.58 (d, J = 9 Hz, 1 H); IR (CH_2Cl_2) 3045, 1765, 1697, 1610 cm^{-1}; MS m/z 284; HRMS calcd 284.06847, measured 284.06826; ^{13}C NMR ($CDCl_3$) δ 24.50, 31.50, 34.90, 44.18, 67.80, 107.65, 112.38, 113.46, 114.82, 118.84, 127.35, 153.05, 155.11, 166.41, 176.54, 200.67; TLC (1:4 H:EA) R_f = 0.16.

Registry No. **5**, 135365-35-4; **6**, 135365-36-5; **7**, 135365-37-6; **9**, 135365-39-8; **10**, 18871-63-1; **12**, 135365-40-1; **13**, 135365-41-2; **14**, 135365-42-3; **15**, 135365-43-4; **16**, 135365-44-5; **17**, 57020-97-0; **18**, 135365-45-6; **19**, 135365-46-7; $MeSSO_2Me$, 2949-92-0; ethyl acetoacetate, 141-97-9; dihydrofuran, 1191-99-7; acetaldehyde, 75-07-0; 1,3-cyclohexanedione, 504-02-9; 2-hydroxy-6-oxo-1-cyclohexene-4-carboxylic acid, methyl ester, 135365-38-7; methyl acetylacetate, 105-45-3.

Supplementary Material Available: Proton NMR data for compounds **5**, **7**, **9**, **12-14**, and **16-18** (19 pages). Ordering information is given on any current masthead page.

Unusual Directive Effects in the Hydroboration of β,β-Disubstituted Enamines. Conversion of α-Substituted Aldehydes to the Corresponding Alkenes and β-Amino Alcohols†

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A comprehensive study of the conversion of β,β-disubstituted enamines into the corresponding alkenes and β-amino alcohols by hydroboration-elimination and hydroboration-oxidation, respectively, has been carried out. The amine moiety of β,β-disubstituted enamines was found to exert a decisive influence on the regioselectivity of the hydroboration reaction involving borane methyl sulfide (BMS). Thus, in the hydroboration of morpholino and piperidino enamines, the boron atom is initially placed predominantly in the α-position. Conversely, the pyrrolidino enamines direct the boron atom exclusively to the β-position. Three oxidizing agents, trimethylamine N-oxide, sodium perborate, and 30% hydrogen peroxide-solid sodium hydroxide, were tried in order to optimize the oxidation of the intermediate organoborane derivatives to the corresponding amino alcohols. Our results clearly indicated that 30% hydrogen peroxide-solid sodium hydroxide is best suited for this transformation. The yield of amino alcohol ranged from good to essentially quantitative. Enamines derived from β-aryl aldehydes, upon hydroboration with BMS followed by methanolysis and oxidation with neutral hydrogen peroxide, gave the corresponding 1,1-disubstituted alkenes. Contrary to the regioselectivity observed in the hydroboration reactions involving BMS, the hydroboration of β,β-disubstituted enamines using 9-borabicyclo[3.3.1]nonane (9-BBN) gave the trialkylborane intermediates in which the boron atom was placed exclusively at the β-position regardless of the amine moiety of the enamine. These trialkylborane derivatives were very stable and did not undergo the usual elimination reaction with either methanol or sodium hydroxide. However, on thermal decomposition, these afforded the corresponding 1,1-disubstituted alkenes in high yields.

Introduction

Many amino alcohols are important therapeutic agents for treating a wide variety of human diseases and disorders.[1] During the last five years, amino alcohols have also become extraordinarily important as chiral auxilliaries in organic synthesis.[2] In attempting to extend the existing methodology for the synthesis of β-amino alcohols[3] and alkenes[4] from enamines to β,β-disubstituted enamines, we discovered an unusual and unexpected directive effect of the amine moiety.

Nearly 25 years ago, the powerful directive effect exerted by a substituent on the hydroboration of substituted vinyl derivatives was thoroughly investigated by Pasto[5] and Brown[6] (Figure 1). The hydroboration of acetoxy- and chloro-substituted vinylic compounds yielded 30-85% of the α-adduct, respectively, while the ethoxy and secondary amino derivatives gave virtually quantitative β-substitution.[6] Additionally, these directive effects were further influenced by varying the parent hydrocarbon skeleton from a butenyl to an isobutenyl system, which resulted in a mixture of α- and β-adducts. Although there is one report that the piperidine enamine of 2-ethylbutyraldehyde gave an α-aminoborane on hydroboration,[4a] the directive effects of the secondary amine moiety in the hydroboration of isobutenyl-type systems has never been investigated systematically. Consequently, we undertook a systematic study of the hydroboration of β,β-disubstituted enamines. During the course of this work on the hydroboration of β,β-disubstituted enamines and the subsequent transfor-

† Dedicated to Professor Joseph Bunnett on the occasion of his retirement.

‡ University of California.

§ The Dow Chemical Company.

(1) Grayson, M., Ed. *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed.; Wiley Interscience: New York, 1982; Vol. 17, pp 311-345.
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(4) (a) Lewis, J. W.; Pearce, A. A. *J. Chem. Soc. B* **1969**, 863. (b) Montury, M.; Gore, J. *Tetrahedron Lett.* **1977**, 219. (c) Froberg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728. (d) Brown, H. C.; Goralski, C. T.; Rangaishenvi, M. V.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 384. (e) Singaram, B.; Rangaishenvi, M. V.; Brown, H. C.; Goralski, C. T.; Hasha, D. L. *J. Org. Chem.* **1991**, *56*, 1543. (f) Goralski, C. T.; Singaram, B.; Brown, H. C. U.S. Patent 4 886 924, 1989. (g) Goralski, C. T.; Singaram, B.; Brown, H. C. U.S. Patent 4 895 996, 1990.
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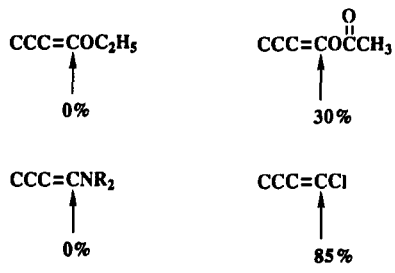


Figure 1. Substituent directive effect in the hydroboration of substituted vinyl derivatives.

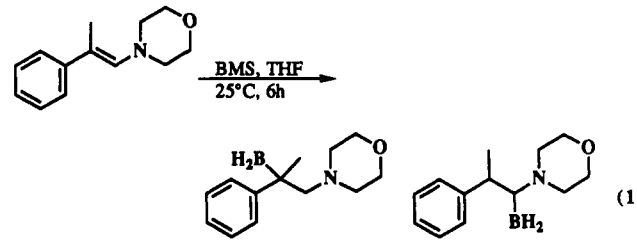
mations of the intermediate organoboranes, a powerful and unexpected directive effect of the amine moiety on the regioselectivity of hydroboration was observed. In addition, we investigated the conversion of β,β-disubstituted enamines into the corresponding alkenes and also sought to extend and optimize the methodology for the synthesis of β-amino alcohols from these enamines by varying the oxidants. We report our findings in this paper.[7]

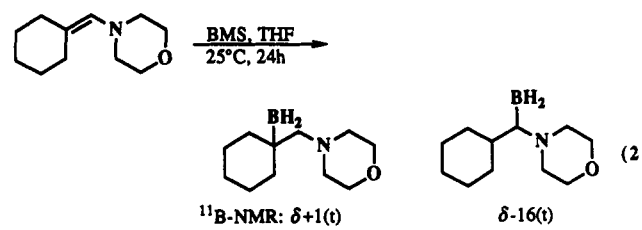
Results and Discussion

Our initial attempt to extend the methodology of alkene synthesis[4d-g] to β,β-disubstituted enamines utilized the following enamines: 2-methyl-1-pyrrolidino-1-pentene, 2-methyl-1-morpholino-1-pentene, 2-phenyl-1-pyrrolidino-1-propene, 1-morpholino-2-phenyl-1-propene, 1,1-diphenyl-2-pyrrolidinoethene, 4-(cyclohexylidenemethyl)morpholine, and 1-(cyclohexylidenemethyl)-pyrrolidine. The enamines were prepared either by stirring a 2:1 mixture of secondary amine and α-substituted aldehyde in cyclohexane with anhydrous potassium carbonate for 24 h at 25 °C, followed by filtration and vacuum distillation of the enamine,[8] or by mixing neat a 2:1 solution of secondary amine and α-substituted aldehyde over 4-Å molecular sieves, followed by transfer to a distillation apparatus under nitrogen and vacuum distillation of the enamine.

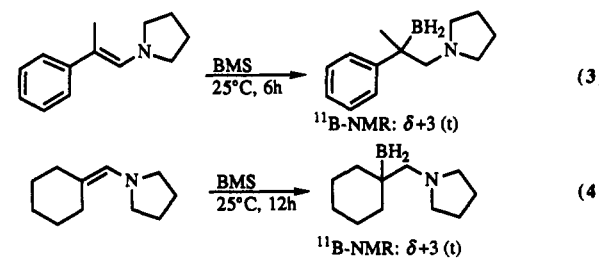
We first attempted the hydroboration of 1-morpholino-2-phenyl-1-propene with 9-borabicyclo-[3.3.1]nonane (9-BBN). Surprisingly, no reaction occurred at 25 °C even after 72 h. We speculated that 9-BBN failed to hydroborate the above enamine due to steric hindrance and tried borane methyl sulfide (BMS) for the hydroboration reaction. When BMS in tetrahydrofuran (THF) was used for the hydroboration of 1-morpholino-2-phenyl-1-propene, we obtained more unexpected results: the ^{11}B NMR spectrum showed two monoalkylborane products. At first, the spectrum consisted of a peak at δ −16 due to an initial kinetic product. At equilibrium, the spectrum consisted of two triplets centered at δ 1 and δ −16 in a ratio of 70:30, respectively. The triplet at δ 1 increased over time, while the intensity of the triplet at δ −16 decreased proportionally to the final ratio of 70:30, respectively. Similarly, the hydroboration of 4-(cyclohexylidenemethyl)morpholine with BMS at 25 °C gave two monoalkylboranes (δ 1 (t), δ −16 (t)). These results were very unusual since only a single monoalkylborane product was expected from these enamines. Additionally, a triplet at δ −16 is an unusual chemical shift for a monoalkylborane–amine complex.[9]

In order to understand these results, we ran the hydroboration of 1-morpholino-2-phenyl-1-propene with BMS in CCl_4 and followed the reaction by both ^1H and ^{11}B NMR. In the ^1H NMR spectrum, the initial kinetic product showed a methyl doublet at δ 1.1 (J = 7 Hz). The intensity of this doublet decreased as a methyl singlet at δ 1.33 appeared and steadily increased in intensity. When all of the enamine olefinic signal disappeared, the ratio of the methyl singlet signal to the methyl doublet signal was 70:30. Concurrent recording of the ^{11}B NMR spectrum showed the appearance of a triplet at δ 1 at the expense of the initial triplet at δ −16. These data clearly showed that, in the hydroboration of β,β-disubstituted enamines, boron is directed initially to both the α- and the β-positions. We assigned the two monoalkylboranes as α- and β-isomers. Similar results were obtained for the hydroboration of 4-(cyclohexylidenemethyl)morpholine with BMS in CCl_4. In this case, the methylene protons of the β-isomer appeared as a singlet (eqs 1 and 2). Contrary





to the results obtained from the morpholino enamines, the pyrrolidino enamines, on hydroboration with BMS at 25 °C, gave a single monoalkylborane product exclusively (eqs 3 and 4). The monoalkylborane product obtained from



2-phenyl-1-pyrrolidino-1-propene exhibited a methyl singlet at δ 1.33 in its ^1H NMR and a triplet at δ 3 in its ^{11}B NMR spectrum.

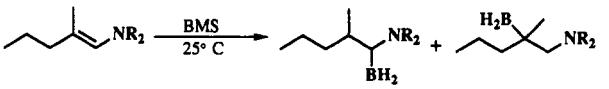
On the basis of these data, we assigned this monoalkylborane as the β-isomer. Apparently, the pyrrolidino moiety directs the boron in the expected manner to the β-position, whereas the morpholino moiety directs the boron to the α-position. Such a directive effect of the dialkylamino group has never been observed before. Consequently, we prepared enamines of 2-methylvaleraldehyde (2-methylpentanal) using various secondary amines and studied their hydroboration with BMS in order to determine the directive effect of these amines. The results are summarized in Table I.

(7) Presented in part at the Seventh International Meeting on Boron Chemistry (IMEBORON VII), Torun, Poland, July 30–Aug 3, 1990, Abstract CB1.

(8) (a) Dulou, R.; Elkik, E.; Veillard, A. *Bull. Soc. Chim. Fr.* **1960**, 967. (b) Stork, G.; Brizzolara, A.; Landesman, H.; Smuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(9) Noth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Springer-Verlag: New York, 1978.

Table I. Directive Effect in the Hydroboration of Enamines Derived from 2-Methylpentanal



amine (NR_2)[a]	α-RBH_2[b]	β-RBH_2[b]
diethylamine	20	80
diisopropylamine	0	100
pyrrolidine	0	100
piperidine	80	20
morpholine	80	20
hexamethyleneimine	10	90

[a] All hydroborations were carried out with solutions of 1 M BMS in THF at 25 °C. [b] Initial kinetic product ratios as determined by ^{11}B NMR spectroscopy. In refluxing THF, the hydroboration is reversible and affords only the thermodynamically more stable β-adduct.

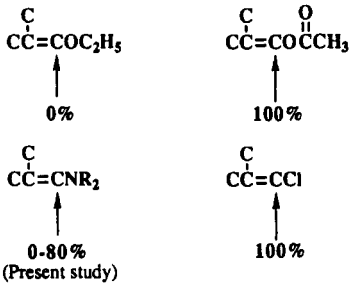


Figure 2. Comparison of the directive effect of secondary amines with that of other substituents in isobutenyl derivatives.

Except for the cyclic, six-membered-ring secondary amines, such as morpholine and piperidine, all amines included in this study initially directed the boron either predominantly or exclusively to the β-position. We can now compare our results with those previously known for the other functionalized isobutenyl derivatives (Figure 2).[5,6] The ethoxy group dominates the directive effect in the hydroboration of the isobutenyl system, placing boron exclusively at the β-position. The directive effect of the acetoxy group and the chlorine atom is small and the hydroboration produces exclusively the α-isomer. One of the surprising developments of this study is the recognition of the unusual directive effect exerted by the dialkylamino group in the hydroboration of β,β-disubstituted (isobutenyl-type) enamines. Thus, six-membered-ring secondary amines have the least directive effect and gave predominantly the α-isomers. All other amines showed a dominant directive effect, leading to the β-isomer. The unexpected α-directing effect of a six-membered cyclic amine moiety in β,β-disubstituted enamines can be explained in much the same way that the rate differences in the reduction of cyclopentanone and cyclohexanone were explained (Figure 3).[10] In pyrrolidino enamines, delocalization of the nitrogen lone pair into an exocyclic double bond, with the concomitant concentration of electron density on the β-carbon, is favored due to the absence of eclipsing interactions in the iminium structure.[11]

This leads to a predominance of β-borane adducts. The opposite is true for the six-membered cyclic amine moieties: the delocalization of the nitrogen lone pair onto the adjacent sp^2 carbon results in an increase of eclipsing interactions and is highly disfavored. Consequently, the

(10) Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221.
(11) (a) Brown, H. C.; Brewster, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1954**, *76*, 467. (b) A detailed review of the structure and reactivity of enamines has recently appeared. Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975.

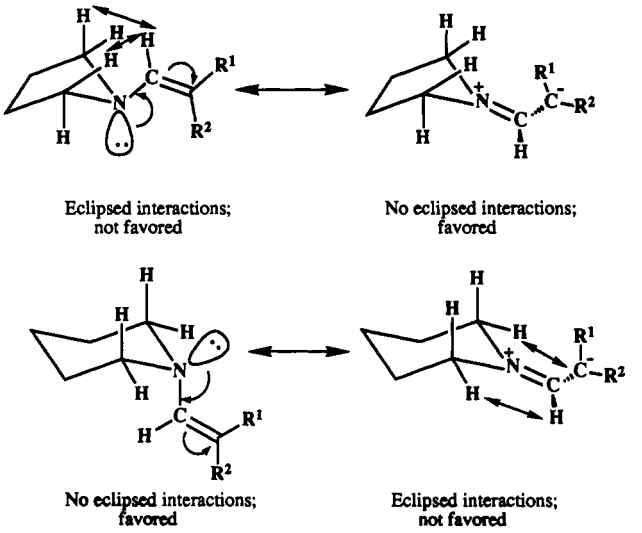


Figure 3. Effect of ring size on the regiochemistry of hydroboration of cyclic amine enamines.

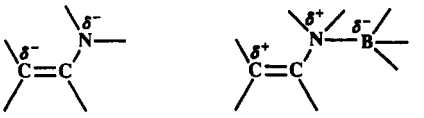
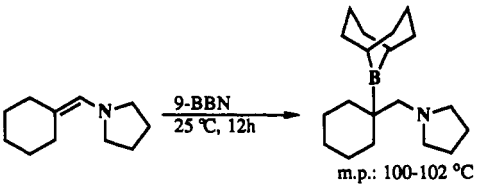


Figure 4. Reversal of the normal electronic effect of the enamine dialkylamino group due to coordination of the hydroboration reagent with nitrogen.

directive effect of the six-membered cyclic amino group is weak and the parent isobutenyl group exerts a dominant directive effect that leads predominantly to the α-adduct. Although steric interactions in β,β-disubstituted enamines should tend to favor the α-borane adducts, the resonance effect shown in Figure 3 clearly outweighs the steric considerations.

We then studied the hydroboration of aliphatic β,β-disubstituted enamines with 9-BBN. Unlike their aromatic counterparts, these enamines were hydroborated at 25 °C within 12 h. Additionally, in spite of the greater steric requirement of the 9-BBN moiety, the boron was directed exclusively to the β-position regardless of the amine moiety of the enamine (eqs 5 and 6).



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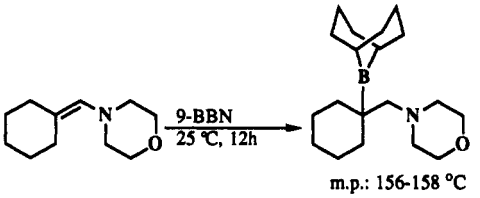


(6)

The normal electronic effect of the dialkylamino group strongly directs the boron to the β-carbon of the enamine.[4] However, if the hydroborating agent initially coordinates at the nitrogen atom, the influence of the dialkylamino group is reversed (Figure 4). One possible explanation is that 9-BBN attacks the enamine double bond without prior coordination with the nitrogen atom, whereas in the case of BMS, initial coordination to the nitrogen atom occurs to a varying degree prior to the hydroboration reaction.

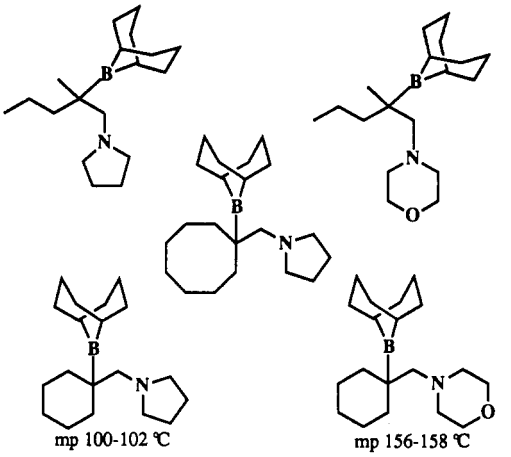
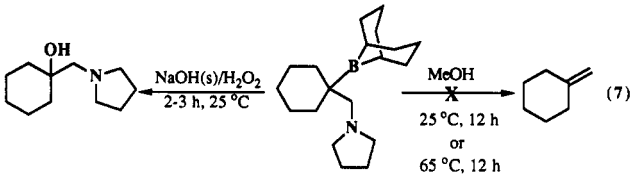


Figure 5. Representative stable 9-BBN trialkylboranes derived from the hydroboration of β,β-disubstituted enamines with 9-BBN.

The following representative trialkylboranes having a β-amino group have been readily synthesized by the hydroboration of the corresponding enamines with 9-BBN (Figure 5). Some of these trialkylboranes are solids and all are stable compounds when stored under an atmosphere of nitrogen. Even the cyclic derivatives do not undergo any appreciable isomerization.[12] Their ^{11}B NMR chemical shifts are in the range of δ 12 to δ 15, indicating that the stability of these trialkylboranes may be attributed to the strong coordination of the boron to the nitrogen atom.

Successful achievement of the hydroboration of β,β-disubstituted enamines prompted us to apply our elimination reaction[4d,e,g] to these organoborane intermediates. Unfortunately, the trialkylboranes obtained from 9-BBN and the β,β-disubstituted enamines failed to react with methanol under conditions that work well for α,β-disubstituted enamines.[4d,e,g] These trialkylboranes were stable toward methanol even at 65 °C and were recovered unchanged (eq 7).



(7)

Fortunately, thermal decomposition of these trialkylboranes afforded the corresponding alkenes. Thus, neat trialkylboranes were maintained at 200 °C for 6 h and the alkenes were isolated in moderate to excellent yield by a simple distillation. The results are summarized in Table II.

The unusual stability of these trialkylboranes also led us to check their reactivity toward the oxidative conditions used earlier to synthesize amino alcohols from the corresponding β- and α,β- substituted enamines.[3c] Accordingly, we oxidized these trialkylboranes using hydrogen peroxide and solid sodium hydroxide. The usual workup afforded the corresponding β-amino alcohols in good yields (Table III).

All of the monoalkylborane intermediates derived from the β,β-disubstituted enamines and BMS reacted readily with methanol to form the corresponding dimethyl boronate esters. However, only the boronate esters derived from the phenyl-containing β,β-disubstituted enamines

Table II. Synthesis of Alkenes from β,β-Disubstituted Enamines

enamine	alkene[a]	yield, %	bp, °C (Torr)
2-phenyl-1-pyrrolidino-1-propene	2-phenyl-1-propene[b]	84	67–69 (20)
1,1-diphenyl-2-pyrrolidino-ethene	1,1-diphenylethene[b]	80	124–126 (6)
2-methyl-1-pyrrolidino-1-pentene	2-methyl-1-pentene[c]	66	60–62 (745)
2-methyl-1-pyrrolidino-1-undecene	2-methyl-1-undecene[c]	80	116–118 (30)
1-(cyclohexylidenemethyl)-pyrrolidine	methylenecyclohexane[c]	82	100–102 (750)

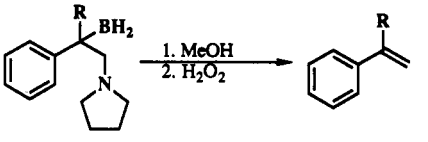
[a] All alkenes reported are commercially available. [b] 1 M BMS in THF; oxidation–elimination with neutral H_2O_2. [c] 10 M 9-BBN in THF; elimination by pyrolysis at 200 °C.

Table III. Synthesis of Amino Alcohols from β,β-Disubstituted Enamines[a]

enamine	amino alcohol[b]	yield,[c] %	bp, °C (Torr)
2-methyl-1-pyrrolidino-1-pentene	2-methyl-1-pyrrolidino-pentan-2-ol[a,e,f]	64	92 (2)
2-methyl-1-morpholino-1-pentene	2-methyl-1-morpholino-pentan-2-ol[d-f]	84	36 (0.1)
1-diethylamino-2 methyl-1-pentene	1-diethylamino-2 methylpentan-2-ol[a,f]	62	70 (0.2)
1-(cyclohexylidenemethyl)pyrrolidine	1-(1-pyrrolidinomethyl) cyclohexanol[a,e]	95	126 (1)
4-(cyclohexylidenemethyl)morpholine	1-(4-morpholinomethyl) cyclohexanol[d,e]	91	143 (0.8)

[a] Hydroboration was carried out using 1 equiv of BMS in THF at 25 °C. [b] All boronate esters were oxidized to the corresponding amino alcohol using NaOH(s)/30% H_2O_2. [c] Isolated yield. [d] Hydroboration was carried out using 1 equiv of BMS in THF at 65 °C for 12 h. [e] Hydroboration was carried out using 1 equiv of 9-BBN in THF at 25 °C for 2–3 h. [f] ^1H NMR showed that a small amount of 2-methyl-1-pentanol was formed as a side product.

underwent oxidative elimination[4d,e,f] with neutral hydrogen peroxide to produce the corresponding alkenes (eq 8). The



(8)

R	
Me	65%
Ph	80%

boronate esters derived from the aliphatic β,β-disubstituted enamines did not produce any detectable amounts of the corresponding alkenes with neutral hydrogen peroxide. Finally, as a proof of structure, we investigated the oxidation of the boronic acid derivatives to the corresponding amino alcohols. Three different oxidizing agents were tried in order to optimize the oxidation of these boronic acid derivatives: trimethylamine *N*-oxide,[13] sodium perborate,[14] and solid sodium hydroxide/30% hydrogen peroxide.[3c] Sodium perborate and trimethylamine *N*-oxide were both experimentally cumbersome. However, solid sodium hydroxide/30% hydrogen peroxide proved to be very

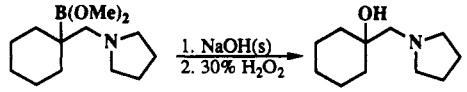
(12) (a) Larson, G. L.; De Jesus, M.; Rosario, O. *J. Organomet. Chem.* **1977**, *132*, 301. (b) Brown, H. C.; Racherla, U. S. *Organometallics* **1982**, *1*, 765.

(13) (a) Koster, R.; Morita, Y. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 580. (b) Kabalka, G. W.; Hedgecock, H. C. *J. Org. Chem.* **1975**, *40*, 1776.

(14) Matteson, D. S.; Moody, R. J. *J. Org. Chem.* **1980**, *45*, 10.

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

straightforward and was the oxidant best suited for the oxidation of these β-amino boronic acid derivatives (eq 9).



(9)

We applied this oxidation procedure to several representative enamines in which both the alkyl and secondary amine moieties were varied. The yield of the corresponding amino alcohols ranged from good to excellent. The results are summarized in Table III.

Conclusion

The present study demonstrates that, in the hydroboration of β,β-disubstituted enamines, the amino group exerts a decisive influence on the regioselectivity of the reaction. Thus, six-membered cyclic secondary amine groups exhibit an unusual directive effect, placing the boron at the α-position to afford the novel α-amino monoalkylboranes as the initial product. Conversely, all other amines included in the present study directed the boron to the β-position as expected. A possible explanation for this unusual directive effect in the hydroboration of β,β-disubstituted enamines is presented. Hydroboration of these enamines with 9-BBN furnished the corresponding trialkylboranes. Conversion of these organoborane intermediates to the corresponding amino alcohols and alkenes is described. Currently, we are actively exploring the asymmetric hydroboration of enamines derived from aldehydes and ketones.

Experimental Section

All operations were carried out under a nitrogen atmosphere. All glassware, syringes, and needles were oven dried at 110 °C and cooled to room temperature with nitrogen gas before use. THF was freshly distilled from sodium and benzophenone ketyl. Anhydrous ether was purchased and used directly. Borane–dimethyl sulfide (BMS, 10 M) and all of the amines and aldehydes were commercial products and used without further purification. ^{11}B NMR spectra were obtained at 300 MHz, and the chemical shifts are in δ units relative to $EE{\cdot}BF_3$ with chemical shifts downfield from $EE{\cdot}BF_3$ assigned as positive. ^1H NMR and ^{13}C NMR were obtained at 300 or 250 MHz. Chemical shifts are in δ units relative to internal Me_4Si.

Synthesis of β,β-Disubstituted Enamines. Method 1.[8] The following procedure is representative. A 500-mL, side-arm, round-bottom flask equipped with a magnetic stirring bar was charged with anhydrous K_2CO_3 (14 g, 100 mmol) and fitted with a reflux condenser. The flask was charged with 2-ethylbutanal (9.5 g, 94.6 mmol), cyclohexane (75 mL), and morpholine (17.4 g, 200 mmol). The heterogeneous reaction was refluxed with stirring for 24 h and cooled to 25 °C, and the supernatant was transferred to a distillation apparatus. The cyclohexane and residual morpholine were removed in vacuo and 2-ethyl-1-morpholino-1-butene was isolated by distillation (9.4 g; 59%, bp 122–123 °C (8 Torr)).

Method 2. The following method is representative. A 500-mL, side-arm, round-bottom flask was charged with 4-Å molecular sieves (3-g sieves per g H_2O predicted), 2-ethylbutanal (31.5 g, 314.4 mmol), and pyrrolidine (44.8 g, 630 mmol). The flask was swirled vigorously for 60 s resulting in a very exothermic reaction. The flask was cooled to room temperature, and the residual pyrrolidine was removed under high vacuum (0.04 Torr) at 25 °C. After the receiving flask was cooled to −78 °C, 2-ethyl-1-pyrrolidino-1-butene was isolated by distillation (36.7 g, 76%; bp 76 °C (6 Torr)).

Conversion of β,β-Disubstituted Enamines to the Corresponding Alkenes. Aromatic Enamines–BMS. The following procedure is representative.[4d,e] To a 1.0 M solution of 1,1-diphenyl-2-pyrrolidinoethene (20 mL, 20 mmol) in THF at 25 °C was added 10.0 M BMS (2.0 mL, 20 mmol) with stirring. The hydroboration was essentially complete after 10 h at 25 °C. The ^{11}B NMR spectrum of the solution indicated the clean formation of a monoalkylborane (δ 1.6, unresolved triplet). Two mL of methanol was added (50 mmol) and the solvent was removed in vacuo. The resulting boronic ester was dissolved in THF to provide a 1.0 M solution. It was oxidized using 30% hydrogen peroxide (2.3 mL, 20 mmol) at 25 °C. The exothermic reaction was controlled by the rate of addition of the hydrogen peroxide and by water bath cooling to maintain the temperature below 30 °C. Water (20 mL) and *n*-pentane (100 mL) was added to the reaction mixture. The organic phase was quickly washed with 3 M HCl (2 × 10 mL) and water (2 × 10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by distillation to give 1,1-diphenylethene (2.9 g, 80%; bp 124–126 °C (6 Torr)).

Aliphatic Enamines–9-BBN. The following procedure is representative. To a stirred suspension of 9-BBN (2.44 g, 20 mmol) in 2 mL of THF at 25 °C was added 2-methyl-1-pyrrolidino-1-pentene (3.07 g, 20 mmol). The reaction mixture became a clear solution after stirring for 3 h. The reaction mixture was stirred for an additional 6 h at 25 °C to ensure complete reaction. The THF was removed in vacuo, the residue heated at 200 °C for 6 h and cooled to 25 °C, and the mixture was distilled. 2-Methyl-1-pentene was collected at atmospheric pressure and further purified by a second distillation (1.1 g, 66%; bp 60–62 °C (745 Torr)).

Synthesis of β-Amino Alcohols from the Corresponding β,β-Disubstituted Enamines. Method 1. The following procedure is representative. 2-Methyl-1-morpholino-1-pentene (1.6 g, 9.6 mmol) was hydroborated, refluxed at 65 °C, and methanolyzed as described above. The boronate ester thus obtained was transferred to a second flask containing solid NaOH (0.42 g, 10.6 mmol). The flask was immersed in a water bath, 30% hydrogen peroxide (1.4 mL, 11.2 mmol) was added dropwise, and the reaction was stirred for 12 h at 25 °C. The clear supernatant was decanted from the white solid and the solid washed with ether (3 × 3 mL). The organic layers were combined and dried over $MgSO_4$. Filtration followed by removal of solvent in vacuo afforded 2-methyl-1-morpholinopentan-2-ol (1.5 g, 84%; bp 58–60 °C (0.07 Torr)).

Method 2. The following procedure is representative. 9-BBN (1.8 g, 15.1 mmol) was added to a side-arm, round-bottom flask equipped with a magnetic stirring bar under N_2 in a glove bag. 1-(Cyclohexylidenemethyl)pyrrolidine (2.4 g, 14.7 mmol) was added followed by THF (3 mL) and the reaction stirred for 2 h at 25 °C. The reaction was diluted to ~1 M with THF. A 10% excess of solid sodium hydroxide (0.7 g, 17 mmol) was added, the flask was immersed in a room-temperature water bath, 30% H_2O_2 (6.1 mL, 49 mmol) was added dropwise, and the reaction was stirred for 2 h. The THF was removed in vacuo and pentane added to the resulting slurry. The reaction was stirred for 30 min, the pentane layer decanted, and the slurry washed with pentane (2 × 3 mL). The organic layers were combined and dried over $MgSO_4$. Filtration followed by removal of solvent in vacuo afforded 1-(1-pyrrolidinomethyl)cyclohexanol (1.8 g, 66%, bp 36 °C (0.09 Torr)).

2-Methyl-1-pyrrolidinopentan-2-ol: ^1H NMR ($CDCl_3$) δ 0.8 (m, 3 H), 1.0 (s, 3 H), 1.2–1.4 (m, 4 H), 1.7 (m, 4 H), 2.4 (dd, J = 13 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 17.1, 24.1, 25.6, 43.6, 56.7, 65.7; m/z 171 (M^+).

2-Methyl-1-morpholinopentan-2-ol: ^1H NMR ($CDCl_3$) δ 0.8 (m, 3 H), 1.1 (s, 3 H), 1.3 (m, 4 H), 2.3 (dd, J = 18 Hz, 2 H), 2.4 (t, J = 1 Hz, 2 H), 2.6 (m, 2 H), 2.8 (s, 1 H), 3.6 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 16, 17.1, 25.4, 43.5, 52, 56, 67, 67.2; m/z 188 ($M^+ + 1$).

1-(Diethylamino)-2-methylpentan-2-ol: ^1H NMR ($CDCl_3$) δ 0.8 (m, 6 H), 0.9 (t, J = 7 Hz, 3 H), 1.0 (s, 3 H), 1.2 (m, 4 H), 2.3 (dd, J = 14 Hz, 2 H), 2.5 (q, J = 7 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 12.2, 14.3, 16.5, 17.1, 20.0, 25.7, 35.5, 43.5, 49.1, 63.2, 68.1; m/z 173 (M^+).

1-(1-Pyrrolidinomethyl)cyclohexanol: ^1H NMR ($CDCl_3$) δ 1.2–1.6 (m, 10 H), 1.7 (m, 4 H), 2.4 (s, 2 H), 2.6 (m, 4 H), 3.8 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.2, 24.1, 25.9, 36.9, 54.6, 56.8, 66.3; m/z 183 (M^+).

1-(4-Morpholinomethyl)cyclohexanol: ^1H NMR ($CDCl_3$) δ 1.2–1.6 (m, 10 H), 2.2 (s, 2 H), 2.5 (m, 4 H), 3.0 (br s, 1 H), 3.6 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 22.1, 24.7, 36.7, 53.5, 56.2, 67.2, 68.2; m/z 199 (M^+).

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Registry No. 2-Ethylbutanal, 97-96-1; morpholine, 110-91-8; 2-ethyl-1-morpholino-1-butene, 28478-26-4; pyrrolidine, 123-75-1; 2-ethyl-1-pyrrolidino-1-butene, 66685-15-2; 1,1-diphenyl-2-pyrrolidinoethylene, 13150-54-4; 1,1-diphenylethene, 530-48-3; (*E*)-2-methyl-1-pyrrolidino-1-pentene, 135310-61-1; (*Z*)-2-methyl-1-pyrrolidino-1-pentene, 135285-83-5; 2-methyl-1-pentene, 763-29-1; (*E*)-2-methyl-1-morpholino-1-pentene, 135285-84-6; (*Z*)-2-methyl-1-morpholino-1-pentene, 135285-85-7; 2-methyl-1-morpholinopentan-2-ol, 135285-86-8; 1-(cyclohexylidenemethyl)pyrrolidine, 6815-55-0; 1-(1-pyrrolidinomethyl)cyclohexanol, 25363-24-0; 2-methyl-1-pyrrolidinopentan-2-ol, 135285-87-9; 2-methylundecanal, 110-41-8; 1-(diethylamino)-2-methylpentan-2-ol, 58124-08-6; 2-methylvaleraldehyde, 123-15-9; 1-(4-morpholinomethyl)cyclohexanol, 116886-08-9; (*E*)-2-phenyl-1-pyrrolidino-1-propene, 66217-90-1; (*Z*)-2-phenyl-1-pyrrolidino-1-propene, 66217-97-8; (*E*)-1-morpholino-2-phenyl-1-propene, 39166-22-8; (*Z*)-1-morpholino-2-phenyl-1-propene, 39173-00-7; 4-(cyclohexylidenemethyl)morpholine, 16963-29-4; (*E*)-2-methyl-1-pyrrolidino-1-undecene, 135285-88-0; (*Z*)-2-methyl-1-pyrrolidino-1-undecene, 135285-89-1; diphenylacetaldehyde, 947-91-1; 2-phenylpropionaldehyde, 93-53-8; cyclohexanecarboxaldehyde, 2043-61-0; cyclooctanecarboxaldehyde, 6688-11-5.

Supplementary Material Available: Physical properties and the spectra of the enamines, alkenes, aminoboranes, and amino alcohols (40 pages). Ordering information is given on any current masthead page.

Synthesis of (±)-Ferruginine and (±)-Anhydroecgonine Methyl Ester by a Tandem Cyclopropanation/Cope Rearrangement

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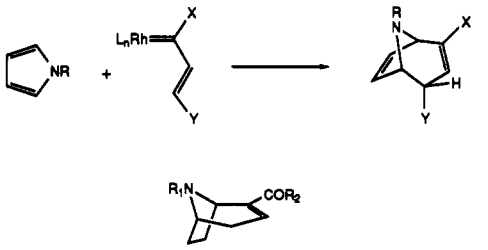
Rhodium(II) acetate catalyzed decomposition of vinyldiazomethanes in the presence of *N*-(alkoxycarbonyl)pyrroles led to the synthesis of 8-azabicyclo[3.2.1]octa-2,6-dienes. The vinylcarbenoids generated from vinyldiazomethanes with a single electron-withdrawing group exhibited competing reactivity at the vinyl terminus in addition to the carbenoid site. Good regiocontrol was possible, however, by appropriate choice of catalyst and solvent. The practicality of this new approach to tropane alkaloids was demonstrated through short syntheses of (±)-ferruginine, (±)-anhydroecgonine methyl ester, and the lower homologue of (±)-anatoxin *a*.

Due to the important bioactivity of the tropane alkaloids, the development of general synthetic procedures to these compounds has been extensively studied.[1] The most notable work in this area has been the pioneering studies of Willstatter[2] and Robinson.[3] Indeed, Robinson's approach based on the condensation of a dialdehyde with methylamine and an acetone derivative is still commonly used.[4] New approaches have been developed such as Noyori's [3 + 4] cycloaddition of iron oxyallyl cations with pyrroles,[5] Tufariello's intramolecular 1,3-dipolar cycloaddition,[6] Kibayashi's nitroso cycloaddition,[7] and Rapoport's imine condensation.[8]

Scheme I



1a $R_1 = H$, $R_2 = OMe$
1b $R_1 = Me$, $R_2 = OMe$
1c $R_1 = H$, $R_2 = Me$
1d $R_1 = Me$, $R_2 = Me$

As part of a program to produce compounds with novel neurochemical activity, we required a general and potentially enantioselective method for the synthesis of tropane derivatives. A new approach based on a tandem cyclopropanation/Cope rearrangement between metal-stabilized vinylcarbenoids and pyrroles[9] appeared to be an attractive strategy as shown in Scheme I. We have previously reported that seven-membered rings may be selectively formed in the reaction of vinylcarbenoids with furans[10] and

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