Hydroboration. 86. Convenient Conversion of Aldehydes and Ketones into the Corresponding Alkenes via Hydroboration of Their Enamines. A Remarkably Simple Synthesis of Either (Z)- or (E)-Alkenes

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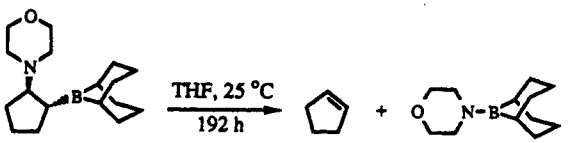
Aldehydes and ketones are converted into the corresponding alkenes via hydroboration of their enamines. Hydroboration of aldehyde enamines by 9-borabicyclo[3.3.1]nonane (9-BBN), followed by methanolysis, affords the corresponding terminal alkenes in 75–90% yields. Unsaturated aldehyde enamines produce the corresponding dienes under these conditions. Enamines derived from substituted cyclic ketones and heterocyclic ketones are readily accommodated in this reaction to afford the corresponding alkenes in very good yields. The synthesis of pure (Z)- or (E)-alkenes is readily achieved from the same acyclic ketone enamine by modification of the hydroboration–elimination procedure: (A) hydroboration by 9-BBN followed by methanolysis or (B) hydroboration by borane methyl sulfide (BMS) followed by methanolysis and hydrogen peroxide oxidation. Mechanistic rationale is provided.

The conversion of carbonyl compounds to alkenes has been of considerable interest in the past and numerous methods have been developed for this transformation.[2-8] In all of these previous studies, except the desulfurization of vinyl sulfides,[5] hydroboration of enamines,[3b] and Shapiro's olefination reaction,[7b] only cyclic ketones in which the stereochemistry of the resulting double bond is fixed have been investigated. However, in the preparation of alkenes from the hydroboration of enamines,[3b] no stereochemistry was given for the starting acyclic enamines or the resulting product alkenes. The reductive dehydration of ketones to form alkenes has also been accomplished in a variety of ways with generally only moderate success.[9] Both alkenes and ketones are fundamental building blocks in organic chemistry since both may be readily transformed into an array of diverse functionality. Thus, reactions that interconvert ketones and alkenes are of vital importance. In the course of expanding our studies on the hydroboration of enamines[10] to include dialkylboranes, we observed certain unusual reactions. Hydroboration of 1-morpholinocyclopentene with 9-borabicyclo[3.3.1]nonane (9-BBN) in tetrahydrofuran (THF) afforded the corresponding trialkylborane cleanly. This trialkylborane, however, slowly underwent elimination upon stirring at 25 °C in THF to give cyclopentene and *B*-morpholino-9-BBN (eq 1). Similar results were obtained with 1-



(1)

morpholinocyclohexene and 9-BBN. When we attempted to oxidize the trialkylborane obtained from 1-morpholinocyclohexene and 9-BBN with alkaline hydrogen peroxide, no amino alcohol could be detected in the product. We later observed that the addition of sodium hydroxide brought about a facile elimination reaction at 25 °C to give cyclohexene. Further studies demonstrated that water and methanol also facilitate this elimination reaction.

The formation of alkenes from enamines has been previously reported in the literature;[3b] however, the reaction conditions were more drastic and the isolation of the highly volatile alkenes difficult. Because of the extremely mild conditions required, we decided to develop the hydroboration–elimination of enamines, employing 9-BBN, as a general procedure for the synthesis of alkenes from carbonyl compounds via enamines. In this paper we describe a simple hydroboration–elimination reaction of enamines derived from acyclic, cyclic, and heterocyclic carbonyl compounds, which permits the facile conversion of aldehydes and ketones into the corresponding alkenes.[11]

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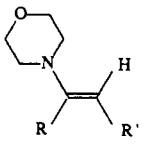
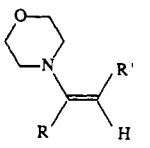
Table I. ^1H NMR[a] Chemical Shifts of the Vinylic Protons of the Morpholine Enamines of Acyclic Ketones



[E] -Isomer



[Z] -Isomer

R	R′	E, δ (ppm)	Z, δ (ppm)
n-propyl	ethyl	4.37	4.68
n-butyl	n-propyl	4.38	4.74
n-pentyl	n-butyl	4.40	4.76

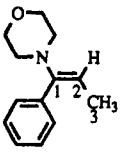
[a] 300 MHz (C_6D_6).

Results and Discussion

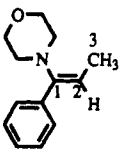
Preparation of Enamines. We selected a wide variety of enamines derived from acylic, cyclic, and heterocyclic ketones for this study. The enamines of aldehydes and ketones were prepared by standard procedures.[12,13] Although p-toluenesulfonic acid is a catalyst for this reaction and was used in several of our reactions, we observed that some reactions were cleaner and the yields of enamine slightly greater when p-toluenesulfonic acid was not used. In the case of enamines derived from cyclic ketones where enamine chemistry has been widely explored, the geometry of the double bond is fixed and we determined their structures by comparing NMR spectral data with literature values.[13] Many enamines have also been prepared from aralkyl ketones, $ArCOCH_2R$, and related heterocyclic ketones and the stereochemistry of the products have been established.[13] However, we could not find any example of a stereodefined enamine derived from a purely aliphatic ketone. We were gratified to find that application of the standard procedure[12] afforded E enamines, >97% pure, even from simple aliphatic ketones.[14] Use of pyrrolidine in the preparation of enamines routinely gave essentially stereochemically pure enamines from most of the ketones used in this study.

The stereochemistry of the enamines derived from aliphatic ketones were determined by NMR spectral analyses. In the case of enamines derived from aliphatic ketones, the major geometric isomer was present in greater than 97%. Since these molecules possess only a single vinyl proton, we applied the NMR additive increment equations developed by Simon et al.[15] and modified by Tobey[16] to predict the chemical shift of the diastereomeric vinyl protons (Table I). Unfortunately, this did not permit an unambiguous assignment of the geometry of these systems and in fact led to incorrect assignment of the lower field signal to the E isomer.[17]

In the case of the morpholine enamine derived from propiophenone, the problem was more acute since the minor isomer was not detected. Application of the NMR additive increment equation to this system predicted shifts of δ 4.46 for the E isomer and δ 4.79 for the Z isomer with



[E]-Isomer



[Z]-Isomer

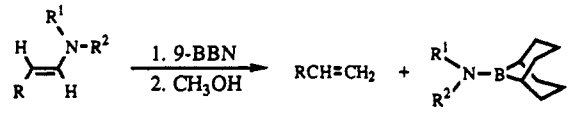
the experimentally observed shift of δ 4.68 being intermediate. Consequently, we determined that this enamine possesses the E configuration based on the predicted two bond carbon–proton coupling between C-1 and the vinyl proton.[18] This coupling cannot be determined directly from the proton-coupled ^{13}C NMR spectrum since the C-1 resonance is a featureless broad peak due to unresolved long-range couplings. The coupling of interest can be extracted by a selective 2D J-resolved experiment (see the Experimental Section).[19] The predicted couplings are 6.5 Hz for the Z isomer and 2.8 Hz for the E isomer, with the measured value being 2.7 Hz.

Table II. Alkenes and Dienes from Aldehyde Enamines

enamine[a]	alkene/diene	yield,[b] %
(E)-1-morpholino-1-octene	1-octene	80
(E)-1-morpholino-3-phenyl-1-propene	3-phenyl-1-propene	82
(E)-1-phenyl-2-pyrrolidinoethene	1-phenylethene	76
(R)-(−)-(E)-1-pyrrolidino-3,7-dimethyl-1,6-octadiene	(R)-(−)-3,7-dimethyl-1,6-octadiene	75
(1E,4E)-1-morpholino-1,4-decadiene	(4E)-1,4-decadiene	82
(1E,4Z)-1-morpholino-1,4-decadiene	(4Z)-1,4-decadiene	89
(E)-1-(hexamethyleneimino)-1,10-undecadiene	1,10-undecadiene	72

[a] Prepared from the corresponding aldehyde and secondary amine in cyclohexane in the presence of anhydrous potassium carbonate. [b] Isolated and distilled.

Terminal Alkenes and Dienes. The general procedure which was developed for the conversion of aldehyde enamines into terminal alkenes consists of the hydroboration of the selected aldehyde enamine with 9-BBN, followed by the addition of one equivalent of methanol to the neat B-[2-(dialkylamino)alkyl]-9-BBN to give an exothermic reaction from which the corresponding terminal alkene distilled. The alkenes thus obtained were often contaminated with trace amounts of methanol, which was easily removed by treatment with anhydrous calcium chloride (eq 2). The reaction is quite general, and the



(2)

results are summarized in Table II. We then explored the possibility of extending this reaction to the synthesis of dienes starting from the corresponding unsaturated aldehydes. In order to achieve this, we needed to know the hydroboration selectivity of 9-BBN toward an enamine double bond and an isolated double bond. Accordingly, we hydroborated a 1:1 mixture of (E)-1-morpholino-1-octene and 1-hexene with 1 equiv of 9-BBN and monitored the reaction by ^1H and ^{11}B NMR spectroscopy. After 3 h at 25 °C, the ^1H and ^{11}B NMR spectrum of the reaction

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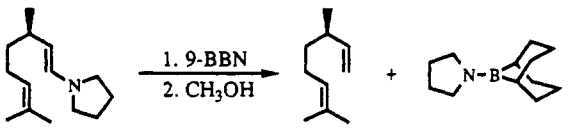
Table III. Cycloalkenes and Substituted Cycloalkenes from Ketone Enamines

enamine[a]	cycloalkene	yield,[b] %
1-morpholinocyclopentene	cyclopentene	82
1-morpholinocyclohexene	cyclohexene	84
1-piperidinocyclohexene	cyclohexene	80
1-(benzylmethylamino)cyclohexene	cyclohexene	75
6-methyl-1-pyrrolidinocyclohexene	3-methylcyclohexene	70
6-cyclohexyl-1-pyrrolidinocyclohexene	3-cyclohexylcyclohexene	75
6-phenyl-1-pyrrolidinocyclohexene	3-phenylcyclohexene	69
1-morpholino-4-*tert*-butylcyclohexene	4-*tert*-butylcyclohexene	72
3,3,5,5-tetramethyl-1-piperidinocyclohexene	3,3,5,5-tetramethylcyclohexene	68

[a] Prepared from the corresponding ketone and secondary amine in toluene. [b] Isolated and distilled.

mixture showed the absence of the enamine olefinic proton signals and the complete utilization of 9-BBN, respectively. It was then methanolyzed and oxidized. Analysis of the reaction mixture showed the presence of a 1:1 mixture of 1-octene and 1-hexene and the absence of 1-hexanol in the product. These results clearly demonstrated the remarkable chemoselectivity of the hydroboration reaction for the electron-rich enamine double bond. Further, this lead us to be optimistic that most other functional groups could be accommodated in this alkene-forming reaction since it has been shown previously[20] that most functional groups are less reactive toward 9-BBN than 1-hexene.

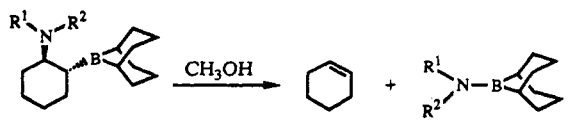
Encouraged by these results, we converted various unsaturated aldehyde enamines into the corresponding dienes (Table II). This hydroboration–elimination reaction has also been applied to enamines derived from citronellal, a chiral aldehyde, to produce a chiral nonconjugated diene, β-citronellene (eq 3).



(3)

75% yield
92% ee
α^{23}_D -6.8° (neat)

Cycloalkenes and Substituted Alkenes. The formation of cycloalkenes and substituted cycloalkenes has been previously described in the literature.[3b] However, the reaction conditions were drastic and the isolation of alkenes difficult. On the other hand, the hydroboration–elimination reaction employing 9-BBN is an extremely mild reaction, and the product alkene is isolated by a simple distillation. Enamines from cyclic ketones, e.g., cyclohexanone, give the corresponding cycloalkenes. The reaction is quite general and enamines derived from various secondary amines can be employed (eq 4).



(4)

75-84%

$-NR^1R^2$ =

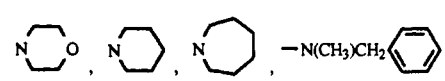


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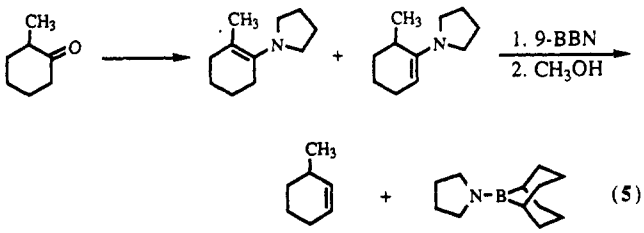
Table IV. Heterocyclic Alkenes from the Corresponding Ketone Enamines

enamine[a]	heterocyclic alkene	yield,[b] %
4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)morpholine	3-cyclohexen-1-one ethylene ketal	75
4-(3,6-dihydro-2*H*-pyran-4-yl)-morpholine[c]	5,6-dihydro-2*H*-pyran	55
4-(3,6-dihydro-2*H*-thiopyran-4-yl)morpholine	5,6-dihydro-2*H*-thiopyan	65
4-(1,2,3,6-tetrahydro-1-benzyl-4-pyridinyl)morpholine	1,2,3,6-tetrahydro-1-benzylpyridine	80

[a] Prepared from the corresponding ketone and morpholine in cyclohexane. [b] Isolated and distilled. [c] Hydroboration was carried out in diethyl ether.

It is known that the formation of pyrrolidine enamines from 2-alkylcycloalkanones is highly regiospecific, providing the less substituted enamines.[21] We took advantage of this fact in converting 2-alkylcycloalkenones into 3-alkylcycloalkenes regiospecifically. For example, 2-methylcyclohexanone was converted to a mixture of 90% 6-methyl-1-pyrrolidinocyclohexene and 10% 2-methyl-1-pyrrolidinocyclohexene, which was subsequently converted, using the general procedure, exclusively into 3-methylcyclohexene (eq 5). Similarly, several representative alkyl

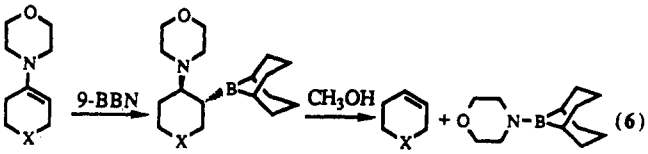


(5)

70% yield
>99% isomeric purity

substituted cyclohexanones were converted into the corresponding alkyl-substituted cycloalkenes (Table III).

Heterocyclic Alkenes. In order to check the generality of this hydroboration–elimination reaction, we included in our study the enamines derived from heterocyclic ketones, such as tetrahydro-4*H*-pyran-4-one, tetrahydro-4*H*-thiopyran-4-one and 1-benzyl-4-piperidinone. The morpholine enamines derived from these ketones, including the piperidinone derivative, underwent hydroboration cleanly with 1 equiv of 9-BBN to furnish the corresponding trialkylboranes. Even though each of these trialkylboranes contains two leaving groups β to the boron atom, only *B*-morpholino-9-BBN is eliminated, producing the corresponding heterocyclic alkenes (eq 6). However, in the case



(6)

X= O, S, $NCH_2C_6H_5$

of the enamine derived from the pyranone, there was ~10% of an acyclic product arising from the boron–oxygen elimination. This side reaction was suppressed by carrying out the reaction in diethyl ether and by reducing the reaction time for the hydroboration stage from 3 to 1 h. These results are summarized in Table IV.

Acyclic (*Z*)- and (*E*)-Alkenes. Finally, we turned our attention to the reaction of 9-BBN with enamines derived

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Table V. (Z)- and (E)-Alkenes from Acyclic Ketone Enamines

enamine[a]	procedure[b]	alkene[c]	yield,[d] %
(E)-1-morpholino-1-phenyl-1-propene	A	(Z)-1-phenyl-1-propene	80
	B	(E)-1-phenyl-1-propene	75
(E)-1,2-diphenyl-1-morpholinoethene	A	(Z)-1,2-diphenylethene	65
	B	(E)-1,2-diphenylethene	80
(E)-1-morpholino-1-(4-pyridyl)-1-propene	A	(Z)-1-(4-pyridyl)-1-propene	60
	B[e]	(E)-1-(4-pyridyl)-1-propene	30
(E)-1-morpholino-1-(2-thienyl)-1-propene	A	(Z)-1-(2-thienyl)-1-propene	68
	B	(E)-1-(2-thienyl)-1-propene	77
(E)-4-pyrrolidino-3-heptane	A	(Z)-3-heptene	69
	B	(E)-3-heptene	50
(E)-5-morpholino-4-nonene	A	(Z)-4-nonene	75
	B	(E)-4-nonene	80
(E)-6-morpholino-5-undecene	A	(Z)-5-undecene	90
	B	(E)-5-undecene	85

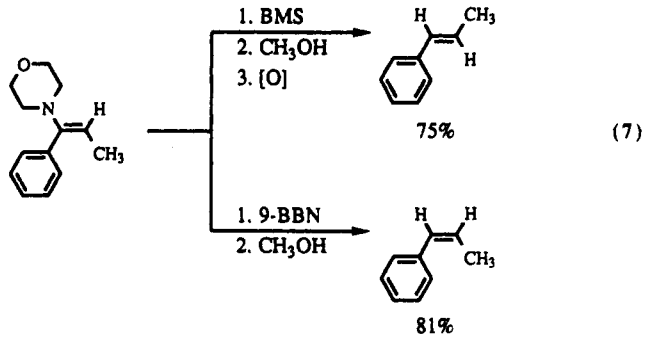
[a] Prepared from the corresponding ketone and secondary amine in toluene. [b] (A) Hydroboration by 9-BBN, followed by methanolysis. (B) Hydroboration by BMS, followed by methanolysis and oxidation with neutral 30% hydrogen peroxide. [c] Stereochemical purity of 99% established by capillary GC and ^{13}C NMR analyses. [d] Isolated and distilled. [e] Alkaline hydrogen peroxide was used.

from acyclic ketones. These enamines also behaved similarly and proved to be the most interesting. Thus, hydroboration–elimination of (E)-1-morpholino-1-phenyl-1-propene[17] with 9-BBN gave 1-phenyl-1-propene in 80% isolated yield. An unexpected bonus from this reaction was the fact that the 1-phenyl-1-propene was the pure Z isomer. Earlier, we had observed in our work on the hydroboration of enamines with borane methyl sulfide (BMS) that (E)-1-morpholino-1-phenyl-1-propene gave the corresponding monoalkylborane, which, on methanolysis, followed by oxidation with alkaline hydrogen peroxide, gave a 35% yield of *threo*-1-morpholino-1-phenyl-2-propanol and a 50% yield of (E)-1-phenyl-1-propene.[10] At that time, this elimination reaction was viewed as an undesirable side reaction, which we suppressed by oxidizing the intermediate with trimethylamine *N*-oxide. Now, this result, coupled with our latest finding with 9-BBN, provides for the first time the methodology for the conversion of an acyclic ketone to either a (Z)- or (E)-alkene via a single enamine derivative.

However, the yield of (E)-1-phenyl-1-propene was less satisfactory, only 50%. Additionally, unlike the elimination reaction involving 9-BBN, the elimination reaction involving the β-amino boronic esters is poorly understood.[10] Consequently, we started a systematic investigation to understand this reaction and to improve the yield of the product (E)-alkene.

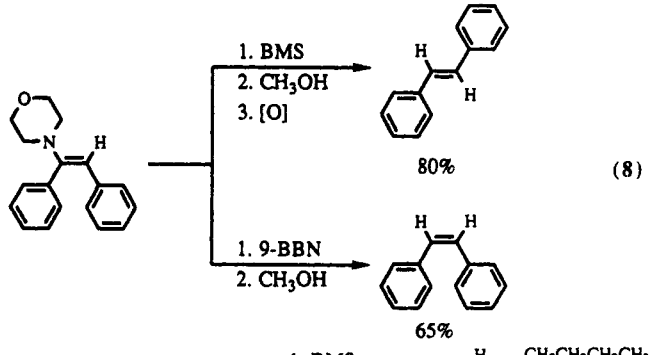
We discovered that sodium hydroxide alone did not induce this elimination reaction in β-amino boronic esters. Sodium hydroxide forms an addition compound with the dimethyl β-amino boronic ester and no further reaction occurs, even after 24 h at 25 °C. We then studied the effect of the oxidizing agents by employing various oxidizing reagents such as neutral hydrogen peroxide, hydrogen peroxide–acetic acid, sodium chlorite, sodium hypochlorite, *tert*-butyl hydroperoxide, *m*-chloroperbenzoic acid, and magnesium monoperphthalic acid. The results from this study revealed that neutral hydrogen peroxide is the best reagent for converting a β-amino boronic ester into (E)-alkene. Our studies also showed that among the various dialkyl β-amino boronic esters studied, the dimethyl ester is the best substrate and THF is the best solvent for this elimination reaction. Thus, when neutral hydrogen peroxide was used as the oxidizing agent for the dimethyl boronate ester derived from (E)-1-morpholino-1-phenyl-1-propene, (E)-1-phenyl-1-propene was obtained in 75% isolated yield.

We now have a truly remarkable chemical situation. The appropriate selection of hydroboration procedures permits for the first time the facile, diastereospecific conversion of a single acyclic ketone enamine into the corresponding (Z)- or (E)-alkene at will. Thus, hydroboration of (E)-1-morpholino-1-phenyl-1-propene by 9-BBN, followed by methanolysis, affords an 80% yield of diastereomerically pure (Z)-1-phenyl-1-propene and hydroboration by BMS, followed by methanolysis and oxidation with neutral hydrogen peroxide, gives a 75% isolated yield of isomerically pure (E)-1-phenyl-1-propene (eq 7).

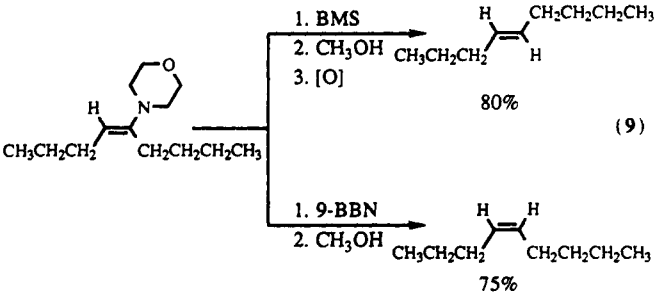


(7)

This methodology was further demonstrated with (E)-1,2-diphenyl-1-morpholinoethene (eq 8),[22] (E)-5-morpholino-4-nonene (eq 9), and various morpholine en-



(8)

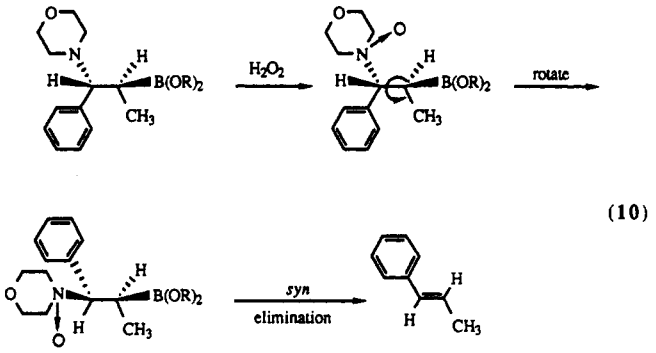


(9)

(22) Munk, M. E.; Kim, Y. K. *J. Org. Chem.* **1965**, *30*, 3705.

amines derived from acyclic ketones. The results are summarized in Table V. The isomeric purity of all of the acyclic alkenes was established by capillary GC and ^1H NMR and ^{13}C NMR analyses.

The mechanisms proposed to account for the stereochemical results obtained from acyclic ketone enamines are shown for (*E*)-1-morpholino-1-phenyl-1-propene. Hydroboration with BMS, followed by methanolysis, gives the corresponding dimethyl boronate ester. The β-amino boronate ester, upon treatment with neutral hydrogen peroxide, affords the amine *N*-oxide, which undergoes syn elimination to give (*E*)-1-phenyl-1-propene (eq 10).

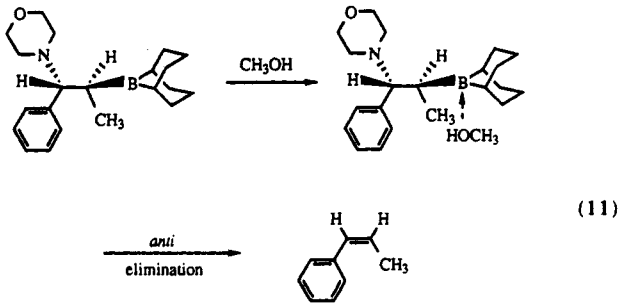


(10)

According to this mechanism, any reagent that can oxidize an amine to the corresponding *N*-oxide should bring about this elimination reaction in amino boronate esters. Indeed, we observed that several other oxidizing agents, such as *m*-chloroperbenzoic acid, magnesium monoperphthalic acid, and *tert*-butyl hydroperoxide, induced this elimination reaction. However, the yield of the alkene was low due to competing side reactions, such as epoxidation of the product alkene and oxidation of the carbon–boron bond. Fortunately, neutral hydrogen peroxide selectively oxidizes an amine to an amine *N*-oxide in the presence of a boronate ester group.

It should be pointed out that previously an anti elimination was observed in the reaction of an enamine with BH_3·THF.[3b] We are reporting for the first time a syn elimination in the hydroboration–elimination reaction of acyclic enamines with BMS.

A possible mechanism for the elimination reaction in the case of the trialkylboranes, *B*-[(dialkylamino)alkyl]-9-BBN derivatives, involves coordination of methanol with the 9-BBN moiety, followed by an anti elimination to produce (*Z*)-1-phenyl-1-propene (eq 11). In contrast, simple



(11)

thermal decomposition of *B-threo*-1-morpholino-1-phenyl-2-propyl-9-BBN affords a 1:2 mixture of (*Z*)- and (*E*)-1-phenyl-1-propene.

Conclusion

Both alkenes and ketones are fundamental building blocks in organic chemistry since both may be readily transformed into an array of diverse functionality. Thus, reactions that interconvert ketones and alkenes are of vital importance. The present study describes a facile conversion of aldehydes and ketones into the corresponding alkenes through the intermediate formation of enamines. Thus, a general synthesis of alkenes and dienes from enamines has been developed in which one equivalent of methanol is added to a neat *B*-[β-(dialkylamino)alkyl]-9-BBN, obtained in essentially quantitative yield from the corresponding enamine and 9-BBN, to give an exothermic reaction from which the alkene or diene can be readily isolated. When applied to the enamines derived from acyclic ketones, (*Z*)-alkenes of 99% isomeric purity were obtained. This result, coupled with an observation that hydroboration of acyclic enamines with BMS, followed by methanolysis and oxidation with neutral hydrogen peroxide gives (*E*)-alkenes of 99% isomeric purity, provides us with the first methods of synthesizing either (*Z*)- or (*E*)-alkenes from a ketone via a single enamine intermediate. The application of these new elimination reactions to the regiospecific and stereospecific synthesis of a number of alkenes and possible mechanisms to account for the observed stereochemistry are also presented.

Experimental Section

All operations were carried out under a nitrogen atmosphere with oven-dried glassware.[23] The spectra were obtained in an inert atmosphere. Gas chromatographic analyses were carried out with a Hewlett-Packard 5750 chromatograph with a TC detector. Capillary gas chromatographic analyses were carried out with a Hewlett-Packard 5890 chromatograph fitted with 50-m methylsilicone or 15-m Supelcowax columns.

NMR Spectra. The NMR spectra were obtained on an IBM AF 300 spectrometer operating at 75.5 and 300 MHz for ^{13}C and ^1H, respectively. The two solvents used in this study were $CDCl_3$ and C_6D_6. It was necessary to use C_6D_6 due to poor stability of some of the enamines in $CDCl_3$. The chemical shifts are referred to tetramethylsilane (TMS). 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.

In order to determine the stereochemistry of the morpholine enamine of propiophenone, the two-bond coupling between the vinyl proton and the C-1 carbon was to be measured. This coupling constant cannot be extracted from the proton-coupled ^{13}C NMR spectrum since additional long-range couplings broaden the C-1 resonance ($\Delta\nu_{1/2} \cong 18$ Hz) obscuring all coupling information. However, the coupling of interest can be determined by conducting a selective 2D *J*-resolved experiment.[19] In this experiment the proton-decoupled carbon spectrum is obtained in one dimension, and the multiplet pattern due to the *selected* proton is found in the other dimension. The proton is *selected* by application of a selective π-pulse midway through the evolution period of the 2D pulse sequence. The π-pulse is made selective by reducing its intensity ($\gamma B_2/2\pi \sim 25$ Hz) and increasing its duration (~20 ms).[24,25] This restricts the spin inversion ability of the π-pulse to a narrow range of frequencies (±25 Hz) centered at the exact resonance condition of the *selected* proton. If the resonances of the *selected* proton are well separated from the other proton resonances (>50 Hz), which is satisfied in the case of the morpholine enamine of propiophenone, only the long-range couplings to the *selected* proton are observed. When this condition is not met or the selective pulse is not an exact π-pulse, a com-

(23) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975.
(24) Freeman, R.; Wittekoek, S. *Proceedings of the XV Colloque Ampere*, Grenoble, 1968.
(25) Freeman, R.; Wittekoek, S. *J. Magn. Reson.* **1969**, *1*, 238.

ponent of carbon magnetization results, which is independent of the coupling due to the *selected* proton, and is proportional to $M_z(1 + \cos \beta_{eff})/2$, where M_z is the equilibrium carbon magnetization and β_{eff} is the effective flip angle of the pulse. This component of the magnetization produces a signal at zero frequency in the coupling dimension of the 2D spectrum. If care is not taken in calibrating the selective π-pulse this signal will interfere in the determination of small couplings, ≤1 Hz.

The π-pulse is calibrated using a 2D version of SEMUT (spectral editing using a multiple trap).[26] This experiment uses the same pulse sequence as the 2D *J*-resolved experiment. However, in the 2D SEMUT experiment the time period corresponding to the evolution period of the 2D *J*-resolved experiment is held constant, adjusted to $(J_{CH})^{-1}$, and the length of the proton pulse is incremented to produce the second frequency dimension. At low decoupler power the resulting 2D spectrum is analogous to the selective 2D *J*-resolved spectrum; the proton-decoupled carbon spectrum is observed in one dimension and the multiplets produced by coupling to the *selected* proton are obtained in the second dimension. Unlike the selective 2D *J*-resolved spectrum, the line separations in the second dimension are not given by the long-range coupling constant but are a measure of the proton (decoupler) field strength. For a separation of νHz, the proton field strength, $\gamma B_2/2\pi$, is given by $\nu/2$ which corresponds to a proton π-pulse equal to $(4\nu)^{-1}$. The selective π-pulse was calibrated using trichloroethylene as the test sample. The constant time period was set to 120.5 ms ($^2J_{CH}$ = 8.3 Hz) and the decoupler power level was varied until a field strength of 33 Hz was obtained. This calibration method resulted in a selective π-pulse with a duration of 30 ms.

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), 1-pyrrolidinocyclopentene, 1-morpholinocyclopentene, and 1-morpholinocyclohexene were purchased from the Aldrich Chemical Co. Other enamines used in this study were prepared by literature methods.[12,13]

Preparation of Styrene from (*E*)-1-Phenyl-2-pyrrolidinoethene. A 50-mL flask equipped with a magnetic stirring bar and a rubber septum was charged with solid 9-BBN (2.44 g, 20 mmol) and THF (5 mL). To this suspension, (*E*)-1-phenyl-2-pyrrolidinoethene (3.46 g, 20 mmol) was added at 25 °C with stirring. After 1 h at 25 °C the reaction mixture became a clear solution. The reaction mixture was stirred for an additional 2 h, and the ^{11}B NMR spectrum indicated the absence of 9-BBN (^{11}B NMR δ +8 ppm, broad singlet). The solvent was removed at 25 °C under reduced pressure (12 Torr). To the solid thus obtained was added methanol (2 mL) containing galvanoxyl (1 mol %). A mildly exothermic reaction occurred, and the reaction mixture was allowed to cool slowly. The byproduct, the pyrrolidine adduct of *B*-methoxy-9-BBN, crystallized from the reaction mixture. *n*-Pentane (100 mL) was added, and the pentane was decanted into a separatory funnel. The pentane solution was quickly washed with 3 N hydrochloric acid (3 × 20 mL) and water (3 × 30 mL) and dried over anhydrous magnesium sulfate. The *n*-pentane was removed by distillation (760 Torr), and the residue was distilled from galvanoxyl (1 mol %) into a flask containing galvanoxyl (1 mol %): 1.58 g (76%); bp 48–50 °C (20 Torr).

Conversion of 1-Morpholinocyclohexene into Cyclohexene. The following procedure for the preparation of volatile cyclohexene is typical. A 50-mL flask equipped with a magnetic stirring bar and a rubber septum was charged with solid 9-BBN (2.44 g, 20 mmol) and THF (4 mL). To this suspension, 1-morpholinocyclohexene (3.55 g, 20 mmol) was added at 25 °C with stirring. After 3 h at 25 °C, the reaction mixture became a clear solution. The ^{11}B NMR spectrum of the solution displayed a broad singlet at δ +82, indicating the clean formation of a trialkylborane. Solvent THF was evaporated under reduced pressure (25 °C, 12 Torr). The reaction flask was then fitted with a distillation head and methanol (0.64 g, 20 mmol) was added to the residue in the flask. There was a mild exothermic reaction, and the whole reaction mixture solidified. Upon heating, the solid melted and cyclohexene, along with methanol, was collected by distillation under atmospheric pressure. The distillate was treated with calcium chloride (1 g) to remove methanol, and the cyclohexene was purified by distillation: 1.38 g (84%); bp 80–82 °C (745 Torr). The ^{11}B NMR spectrum of the pot residue showed a singlet at δ +47 due to *B*-morpholino-9-BBN.

Preparation of 3-Cyclohexylcyclohexene from 6-Cyclohexyl-1-pyrrolidinocyclohexene. The following procedure for the conversion of an enamine into a nonvolatile alkene is representative. A 100-mL flask equipped with a magnetic stirring bar and a rubber septum was charged with solid 9-BBN (2.44 g, 20 mmol) and THF (4 mL). To this slurry was added 6-cyclohexyl-1-pyrrolidinocyclohexene (4.67 g, 20 mmol) at 25 °C with stirring. After 3 h at 25 °C, the reaction mixture became a clear solution. Solvent THF was evaporated under reduced pressure (25 °C, 12 Torr). Methanol (1.0 mL, 25 mmol) was added to the residue and gently warmed with a heat gun. An exothermic reaction occurred, and the reaction mixture solidified. The solid was triturated with *n*-pentane (3 × 20 mL). The *n*-pentane layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure (25 °C, 12 Torr). The residue was purified by distillation to give 3-cyclohexylcyclohexene: 2.46 g (75%); bp 124–126 °C (20 Torr).

Hydroboration of a 1:1 Mixture of 1-Hexene and 1-Morpholino-1-octene with 1 equiv of 9-BBN. A 50-mL flask was charged with a CCl_4 solution of 9-BBN (0.5 M, 10 mmol). To this, 1-hexene (10 mmol), 1-morpholino-1-octene (10 mmol), and internal standard benzene (5 mmol) were added with stirring. An aliquot (0.6 mL) was withdrawn into an NMR tube, and the reaction was monitored by ^{1}H and ^{11}B NMR spectroscopy. Hydroboration was complete in 3 h, as evidenced by the disappearance of 9-BBN signal (s, δ +27) in the ^{11}B NMR spectrum. The ^{11}B NMR spectrum displayed a broad singlet at δ +87 due to the formation of a trialkylborane. The ^{1}H NMR spectrum showed the quantitative utilization of the enamine double bond whereas 1-hexene remained unchanged.

In a separate experiment, a 100-mL flask was charged with 9-BBN (10 mmol), 1-hexene (10 mmol), 1-morpholino-1-octene (10 mmol), and THF (10 mL). To this, *n*-hexadecane (5 mmol) was added as an internal standard. After 3 h at 25 °C, 1 equiv of methanol was added. The ^{11}B NMR spectrum showed a peak at δ +56 due to *B*-methoxy-9-BBN. This clearly showed that the trialkylborane formed in this reaction was not *B*-*n*-hexyl-9-BBN. The reaction mixture was then oxidized with alkaline hydrogen peroxide. Gas chromatographic analysis showed the presence of a 1:1 mixture of 1-hexene and 1-octene and no 1-hexanol was present in the product.

Synthesis of 1,10-Undecadiene from the Corresponding Enamine. The following procedure for the synthesis of 1,10-undecadiene is illustrative. A 50-mL flask equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser was charged with solid 9-BBN (1.22 g, 10 mmol) and THF (2 mL). To this slurry was added 1-morpholino-1,10-undecadiene with stirring. After 3 h at 25 °C, the solvent THF was evaporated (25 °C, 12 Torr). Methanol (10 mmol) was added to the residue, and the mixture was refluxed for 1 h. The reaction mixture was cooled to 25 °C, and the reflux condenser was replaced by a distillation head. The product was collected by distillation under reduced pressure. The distillate was treated with calcium chloride (1 g) to remove any methanol present, and 1,10-undecadiene was purified by distillation: 1.1 g (72%); bp 78–80 °C (15 Torr).

Preparation of 5,6-Dihydro-2*H*-thiopyran from 4-(3,6-Dihydro-2*H*-thiopyran-4-yl)morpholine. The following procedure for the synthesis of the heterocyclic alkene, 5,6-dihydro-2*H*-thiopyran, is representative. The solid enamine (3.7 g, 20 mmol) was dissolved in THF (10 mL), and this solution was added to solid 9-BBN (2.44 g, 20 mmol) with stirring. The suspension became a clear solution after 3 h at 25 °C, and the solvent THF was evaporated under reduced pressure (25 °C, 12 Torr). Methanol (0.8 g, 25 mmol) was added to the residue and gently warmed with a heat gun. An exothermic reaction occurred, and the reaction mixture solidified. The solid was triturated with *n*-pentane (3 × 20 mL). The *n*-pentane solution was decanted and washed successively with water (2 × 10 mL), 3 N sodium hydroxide (3 × 10 mL), 3 N hydrochloric acid (3 × 10 mL), and water (2 × 10 mL) to remove *B*-methoxy-9-BBN and morpholine. The *n*-pentane layer was dried over anhydrous magnesium sulfate,

(26) Nielsen, N. C.; Bildsoe, H.; Jakobsen, H. J.; Sorensen, O. W. *J. Am. Chem. Soc.* **1987**, *109*, 901.

and the solvent was evaporated under reduced pressure (25 °C, 12 Torr). The residue was purified by distillation to give 5,6-dihydro-2*H*-thiopyran: 1.31 g (65%); bp 58–60 °C (20 Torr).

Synthesis of (*Z*)-1-Phenyl-1-propene from (*E*)-1-Morpholino-1-phenyl-1-propene. The following procedure (A) for the preparation of (*Z*)-1-phenyl-1-propene is illustrative. To a stirred suspension of 9-BBN (2.44 g, 20 mmol) in THF (4 mL) was added (*E*)-1-morpholino-1-phenyl-1-propene (4.06 g, 20 mmol). The suspension became a clear solution after 3 h at 25 °C. The ^{11}B NMR spectrum of the solution indicated the absence of 9-BBN. The solvent THF was evaporated under reduced pressure (25 °C, 12 Torr). Methanol (0.8 g, 25 mmol) was added to the residue. A mildly exothermic reaction occurred, and the reaction mixture solidified. The solid was triturated with *n*-pentane (3 × 20 mL). The *n*-pentane solution was decanted and washed successively with water (2 × 10 mL), 3 N sodium hydroxide (3 × 10 mL), 3 N hydrochloric acid (3 × 10 mL), and water (2 × 10 mL) to remove *B*-methoxy-9-BBN and morpholine. The *n*-pentane layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure (25 °C, 12 Torr). The residue was purified by distillation to give isomerically pure (*Z*)-1-phenyl-1-propene: 1.90 g (81%); bp 62–64 °C (12 Torr).

Preparation of (*E*)-1-Phenyl-1-propene from (*E*)-1-Morpholino-1-phenyl-1-propene. The following procedure (B) for the preparation of (*E*)-1-phenyl-1-propene is typical. To a 1.0 M THF solution of (*E*)-1-morpholino-1-phenyl-1-propene (20 mL, 20 mmol), borane–methyl sulfide (2.0 mL, 20 mmol), was added at 25 °C with stirring. A yellow color developed immediately and faded completely within 0.25 h. The reaction mixture was stirred at 25 °C for 1 h and then methanolyzed. The solvent was evaporated under reduced pressure (25 °C, 12 Torr), and the resulting crude boronate ester was dissolved in THF so as to give a 1.0 M solution. It was oxidized using 30% hydrogen peroxide (2.3 mL), and the exothermic reaction was controlled by the rate of addition and by water-bath cooling to maintain the temperature below 30 °C. After 2 h, water (20 mL) and *n*-pentane (100 mL) were added to the reaction mixture. The organic phase was quickly washed with 3 N HCl (2 × 10 mL) and water (2 × 10 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated (25 °C, 12 Torr), and the residue was purified by distillation to give isomerically pure (*E*)-1-phenyl-1-propene: 1.77 g (75%); bp 72–74 °C (20 Torr).

Acknowledgment. We thank the Dow Chemical Company for financial support of this work.

Supplementary Material Available: Physical properties and the spectra of the enamines used in this study are available as supplementary data (20 pages). Ordering information is given on any current masthead page.

Synthesis of Rotationally Restricted Tetrahydrocannabinol Ethers

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Two rotationally restricted tetrahydrocannabinol (THC) ethers were synthesized to test the concept that the psychopharmacological activity of cannabinoids derives, in part, from the orientation of the lone pairs of electrons of the phenolic hydroxyl oxygen. These compounds, *O*,2-propano-Δ^8-THC (**3**) and *O*,10-methano-Δ^9-THC (**12**), lock the orientation of the lone pairs of electrons toward and away from the cyclohexene ring, respectively, by restricting bond rotation through the formation of cyclic ethers. The synthesis of **3** was achieved by alkylation of the phenolic oxygen of Δ^8-THC (**1**) with 3-bromo-1-propanol followed by cyclodehydration in the presence of phosphorus pentoxide. The synthesis of **12** was achieved from a sequence of reactions that involved the cyclization of a chloroformate in a modification of the Darzens acylation of olefins. Thus, treatment of Δ^9-THC with phosgene in the presence of *N*,*N*-dimethylaniline afforded Δ^9-THC chloroformate. Subsequent intramolecular cycloaddition of the chloroformyl moiety to the Δ^9-unsaturation in the presence of $AlCl_3$ afforded the corresponding β-chloro ester **9**. Treatment of **9** with lithium aluminum hydride gave 10-(hydroxymethyl)-Δ^9-THC (**10**). Compound **12** and 10-methylene-Δ^8-THC (**11**) were obtained as a readily separable mixture by treatment of **10** with 3 mol of tosyl chloride in pyridine. ^{13}C NMR and ^1H NMR spectral assignments were made. A model study of the $TiCl_4$-mediated cleavage of the MEM ether of phenol demonstrated generation of the phenoxymethyl cation.

Two rotationally restricted tetrahydrocannabinol (THC) ethers were synthesized to test the hypothesis that the psychopharmacological activity of cannabinoids derives, in part, from the orientation of the lone pairs of electrons of the phenolic hydroxyl oxygen. Previous theoretical studies[2] have indicated that there are two minimum energy positions for the phenol hydroxyl in (−)-Δ^9-THC (**7**), the major psychopharmacologically active component of cannabis.[3] In these conformations, the lone pairs of electrons on the C1 oxygen are oriented toward and away from the cyclohexane ring. The two rotationally restricted THC ethers discussed here were designed to mimic the two phenol conformations of (−)-Δ^9-THC. Thus, *O*,2-propano-Δ^8-THC (**3**) and *O*,10-methano-Δ^9-THC (**12**) orient the lone pairs of electrons toward and away from the cyclohexane ring, respectively, by restricting bond rotation through the formation of cyclic ethers.

The accessible conformations of both **3** and **12** were calculated by using the method of molecular mechanics as encoded in the MMP2(85) program.[4] For **3**, two accessible minimum energy conformers were found that differend principally in the conformation of the new fourth ring. In the global minimum structure, the chroman ether

(1) (a) Research Triangle Institute. (b) Organon Teknika, NC. (c) Amgen, CA. (d) Kennesaw State College.

(2) (a) Reggio, P. H.; Mazurek, A. P. *J. Mol. Struc. (Theochem.)* **1987**, *149*, 331. (b) Reggio, P. H.; Greer, K. V.; Cox, S. M. *J. Med. Chem.* **1989**, *32*, 1630.

(3) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1971**, *93*, 217.

(4) Allinger, N. L. MMP2(85), distributed by Molecular Design, Ltd., San Leandro, Ca.

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