between the $\alpha$-fluorine and nitrogen splittings are both 1 gauss, one would expect to see seven additional lines of 1:5.5:13:17:13:5.5:1 relative intensity. The measured heights of the seven observed lines on the central peak were 1:4.7:7.2:8.3:7.3:5.2:1.2. The low values for these peaks again may be due to the inhomogeneous line broadening because of inequality of the above splittings. In fluorocarbon nitroxides, the fluorine bonded to the $\beta$-carbon are believed to give splittings of about 1 gauss, while the nitrogen and fluorine bonded to the $\alpha$-carbon give about equal splitting and can be expected to be in the 8–11-gauss range.

The $\alpha$-fluorine and nitrogen splitting in $(C_7F_{15})_2NO$ appear to be much closer than they are in $(ClCF_2CF_2)_2NO$, based on the rather close agreement of the measured peak heights in the e.s.r. spectra to the expected values. In addition, five equally spaced lines of slightly less than 1-gauss separation were observed on all seven major peaks and were attributed to the interactions of the four equivalent $\beta$-fluorine atoms. The relative peak heights of the five peaks are in good agreement with the expected values. The e.s.r. spectra furnish good evidence for the existence of stable higher nitroxides containing perfluoroalkyl substituents.

The complex spectra obtained on the addition of any of the radicals to ether was believed to result from the formation of a new radical species and not a solvent effect.

The e.s.r. data, mass spectroscopic analysis, molecular weight, fluorine analysis, and reaction with nitric oxide establish the structure of the first radical material as that proposed, bis(2-chlorotetrafluoroethyl) nitroxide. The e.s.r. results indicate the existence of other stable nitroxides containing fluorocarbon substituents with up to 7 carbons in the chain. It is believed that fluorocarbon nitroxides are a stable class of free-radical species. The loss of a fluorine from each of the $\alpha$-carbons and replacement with a fluorocarbon group did not significantly affect the stability of the nitroxide. As the fluorine is replaced by larger fluoroalkyl groups, any loss in stabilization by decreased electron delocalization may be balanced by an increase in the stabilization by steric effects. The radical $(ClCF_2CF_2)_2NO$ did not appear to dimerize on cooling, as $(CF_3)_2NO$ did, indicating possible steric repulsions by the larger chlorotetrafluoroethyl groups.

**Acknowledgments.** The author wishes to express thanks to Drs. Harry Chafetz and Russell R. Reinhard for their helpful discussion, to Mr. Lee M. Huber for help in interpretation of the e.s.r. data, and to Mr. Joseph DiLandro for his assistance with the experimental work.

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# Synthesis of Functionally Substituted Alkylboronic Acids. Hydroboration of N-Alkenylureas and -carbamates[1]

**D. N. Butler[2] and A. H. Soloway**

*Contribution from the Neurosurgical Research Laboratories, Massachusetts General Hospital, Boston, Massachusetts.* *Received September 21, 1965*

**Abstract:** In contrast with terminal hydrocarbon olefins, the hydroboration of certain N-alkenylureas and N-alkenylcarbamates ceases to an appreciable extent at the monoalkylborane stage. This is indicated by the hydrolysis of these intermediate organoboranes to the corresponding substituted aminoalkylboronic acids.

The preparation of a variety of functionally substituted alkylboronic acids has been limited as a result of the incompatibility between the previous synthetic methods for introducing the boronic acid moiety and the desired functional groups. To circumvent this difficulty, Matteson[3] introduced functional groups into ethylenic and acetylenic boronic acids esters by radical additions. Recently the application of the hydroboration reaction to functionally substituted olefins has led to the synthesis of several substituted alkylborons,[4] some novel boron heterocycles,[5] and alcohols resulting from the oxidation of borane intermediates.[6] This latter work has demonstrated the feasibility of this reaction in the presence of certain functional groups including some that are normally reduced by diborane. However, the extreme reactivity of unhindered monoalkylboranes to undergo further hydroboration to trialkylborons[4] appeared to preclude the general synthesis of boronic acids by this method, though the utility of this reaction for the synthesis of such compounds had been indicated.[7]

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[1] This research was supported by grants from the John A. Hartford Foundation, Inc., U. S. Atomic Energy Commission AT(30-1)-3267, and U. S. Public Health Service CA-07368. Preliminary reports have appeared: D. N. Butler and A. H. Soloway, *J. Am. Chem, Soc.*, **86**, 2961 (1964); *Chem. Comm.*, **15**, 333 (1965).

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[3] D. S. Matteson, *J. Am. Chem. Soc.*, **82**, 4228 (1960).

[4] For a review of this area see H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

(5) (a) M. F. Hawthorne, *J. Am. Chem. Soc.*, **82**, 748 (1960); (b) M. F. Hawthorne, *ibid.*, **83**, 2541 (1961); (c) D. G. White, *ibid.*, **85**, 3634 (1963); (d) N. N. Greenwood, J. H. Morris, and J. C. Wright, *J. Chem. Soc.*, 4753 (1964); (e) M. J. S. Dewar, G. T. Gleicher, and B. P. Robinson, *J. Am. Chem. Soc.*, **86**, 5698 (1964); (f) N. N. Greenwood and J. C. Wright, *J. Chem. Soc.*, 448 (1965); (g) R. M. Adams and F. D. Poholsky, *Inorg. Chem.*, **2**, 640 (1963).

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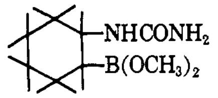
Table I. Hydroboration of N-Vinylamine Derivatives

| Product no. | Product | Starting material | M.p.[a] or b.p. (mm.), °C. | Formula | Anal., % | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calcd. | | | | Found | | | |
| | | | | | C | H | N | B | C | H | N | B |
| V | $NH_2CONHCH_2CH_2B(OCH_3)_2$ | N-Vinylurea | 65–68 | $C_5H_{13}BN_2O_3$ | 37.54 | 8.19 | 17.52 | 6.76 | 37.81 | 8.20 | 17.72 | 6.85 |
| III | $NH_2COCHCH_2CH_2B(OH)_2$ | | 102–104 | $C_3H_9BN_2O_3$ | 27.30 | 6.88 | 21.25 | 7.64 | 27.35 | 6.92 | 21.30 | 7.84 |
| VI | Imminodiethanol deriv. of III | | 237–238 | $C_7H_{16}BN_3O_3$ | 41.82 | 8.02 | 20.89 | 5.38 | 42.10 | 8.14 | 21.10 | 5.71 |
| VII | $NH_2CONHCH_2CH(CH_3)B(OH)_2$ | N-1-Propenylurea | 115–117 | $C_4H_{11}BN_2O_3$ | 32.91 | 7.59 | 19.20 | 7.41 | 32.69 | 7.84 | 19.30 | 7.20 |
| VIII | Imminodiethanol deriv. of VII | | 229–230 | $C_8H_{18}BN_3O_3$ | 44.68 | 8.44 | 19.54 | 5.03 | 44.88 | 8.71 | 19.31 | 4.98 |
| IX |  | N-1-Cyclohexenylurea | 145–147 | $C_9H_{19}BN_2O_3$ | 50.67 | 8.98 | 13.14 | 5.07 | 50.64 | 9.13 | 13.10 | 5.20 |
| X |  | | Indef. | $C_7H_{15}BN_2O_3$ | 45.21 | 8.13 | 15.87 | 5.82 | 45.48 | 8.16 | 14.98 | 6.19 |
| XI | Imminodiethanol deriv. of X | | 225–227 | $C_{11}H_{22}BN_3O_3$ | 51.78 | 8.69 | 16.47 | 4.24 | 51.50 | 8.47 | 16.14 | 4.42 |
| XII | $C_2H_5OCONHCH_2CH_2B(OCH_3)_2$ | | 84–88 (0.35)[b] | $C_7H_{16}BNO_4$ | 44.48 | 8.51 | 7.41 | 5.72 | 44.39 | 8.82 | 7.64 | 5.82 |
| XIII | $C_2H_5OCONHCH_2CH_2B(OH)_2$ | Ethyl N-vinylcarbamate | 71–73 | $C_5H_{12}BNO_4$ | 37.32 | 7.52 | 8.70 | 6.72 | 37.45 | 7.73 | 8.52 | 6.90 |
| XIV | Imminodiethanol deriv. of XIII | | 168–169 | $C_9H_{19}BN_2O_4$ | 46.98 | 8.32 | 12.18 | 4.70 | 46.77 | 8.56 | 12.02 | 4.97 |
| XV | $C_6H_5CH_2OCONHCH_2CH_2B(OH)_2$ | Benzyl N-vinylcarbamate | 106–108 | $C_{10}H_{14}BNO_2$ | 53.84 | 6.33 | 6.28 | 4.85 | 53.61 | 6.29 | 6.56 | 5.12 |
| XVI | Imminodiethanol deriv. of XV | | 159–161 | $C_{14}H_{21}BN_2O_4$ | 57.55 | 7.25 | 9.59 | 3.70 | 57.26 | 7.00 | 9.46 | 3.98 |

[a] The melting points of boronic acids are unreliable: W. Gerrard, "The Organic Chemistry of Boron," Academic Press Inc., New York, N. Y., 1961, p. 68. [b] Decomposition occurs during distillation.

Recently aliphatic boronic acids have been prepared[8] by the hydroboration procedure, but the mechanism by which the reaction stops at the monoalkylborane remains unclear. It is conceivable, however, that there is stabilization of the initially formed monoalkylborane intermediates. The hydroboration of the N-olefin-substituted ureas and carbamates described in this paper has indicated strongly the presence of such internally coordinated intermediates and has allowed the preparation of several novel substituted aminoalkylboronic acids required in connection with the current boron neutron-capture cancer therapy program underway in these laboratories.[9]

## Results

**Hydroboration of N-Vinylamine Derivatives.** When N-vinylurea in tetrahydrofuran was added to an excess of diborane in the same solvent at 0°, followed by the addition of methanol to decompose any excess diborane and the intermediate alkylborane, **dimethyl β-ureidoethylboronate** (Va) was obtained in 80% yield. Hydrolysis of this hygroscopic ester with water then afforded **β-ureidoethylboronic acid** (III). Use of this procedure on several other substituted N-vinylureas and carbamates effected entirely similar results with good yields of the corresponding alkylboronic acids. The relevant information is tabulated in Table I. The iminodiethanol derivatives of these boron compounds were prepared in each case by treatment of the acid in dimethylformamide with iminodiethanol. 1,2-Diureidoethylene and N-*trans*-2-chlorovinylurea were also synthesized and subjected to the same hydroboration reaction conditions, but no substituted ethylboronic acids could be detected in the reaction mixtures.

The position of the introduced boron atom in all these examples is clearly shown by the p.m.r. spectroscopy in $D_2O$. The compounds III, XIII, and XV all show two triplets, each triplet being assigned to the two protons of each methylene moiety. The methylene protons adjacent to the nitrogen atom absorb near 3.2 p.p.m. and those next to the boron atom near 1.1 p.p.m. ($J \approx 7$ c.p.s.) indicating their common 1,2-disubstituted ethane structure. In no case was there any evidence for the formation of 1,1-disubstituted compounds as was observed in the hydroboration of dibutyl ethyleneboronate.[8]

**Hydroboration of N-Allylamine and N-Butenylamine Derivatives.** The application of the above procedures to N-allylurea and ethyl and benzyl N-allylcarbamates afforded mixtures corresponding to the introduction of the boronic acid function in positions 2 and 3 to the nitrogen atom. From the p.m.r. spectra of these mixtures it was not possible to estimate accurately the proportions of each isomer, but as much as 30–50% of the total product corresponded to the addition of boron to the nonterminal carbon atom of the double bond. Over-all yields were less (30–40%) than were obtained in the vinylamine examples. From these mixtures, **3-ureidopropylboronic acid** (XVII) (as the imminodiethanol derivative) and **3-benzyloxycarbamidopropylboronic acid** (XIX) were isolated as pure compounds as shown (see Table II) by their p.m.r. spectra.

The hydroboration of N-but-3-enylurethan took a similar course with a low yield (15%) of a mixture of the 3- and 4-boronic acid methyl esters being obtained after methanolysis.

## Discussion

The hydroboration of unhindered terminal hydrocarbon olefins proceeds to the trialkylboron derivatives even in the presence of a large excess of diborane.[4] This is certainly indicative that monoalkylboranes are much more efficient hydroborating agents than borane itself. However, in the case of ureido- or carbamato-substituted olefins, high yields of alkylboronic acids were obtained after hydrolysis, indicating an appreciably lower reactivity of such substituted monoalkylboranes. This is not explainable on the basis of the

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Table II. Hydroboration of N-Allylamine Derivatives

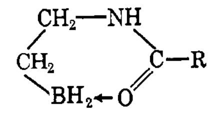
| Product no. | Product | Starting material | M.p.[a] or b.p. (mm.), °C. | Formula | Anal., % Calcd. C | H | N | B | Found C | H | N | B |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XVII | $NH_2CONHCH_2CH_2CH_2B(OH)_2$<br>Imminodiethanol deriv. | N-Allylurea | 220–221 | $C_8H_{18}BN_3O_3$ | 44.68 | 8.44 | 19.54 | 5.03 | 44.70 | 8.45 | 19.30 | 5.09 |
| XVIII | $C_2H_5OCONO(CH_2)_3B(OCH_3)_2$ +<br>$C_2H_5OCONHCH_2CHB(OCH_3)_2CH_3$ | Ethyl N-allylcarbamate | 101–105 (0.3)[b] | $C_8H_{18}BNO_4$ | 47.32 | 8.93 | 5.90 | 5.33 | 47.35 | 8.93 | 7.31 | 5.30 |
| XIX | $C_6H_5CH_2OCONHCH_2CH_2CH_2B(OH)_2$ | Benzyl | 76–84 | $C_{11}H_{16}BNO_4$ | 55.73 | 6.80 | 5.91 | 4.56 | 55.83 | 6.63 | 5.77 | 4.90 |
| XX | Imminodiethanol deriv. of XIX | N-allylcarbamate | 167–168 | $C_{15}H_{23}BN_2O_4$ | 58.84 | 7.57 | 9.15 | 3.62 | 59.21 | 7.60 | 9.02 | 3.47 |

[a] See Table I, footnote *a*. [b] Some decomposition occurs during distillation.

inductive effect of the substituents but can be accounted for by an internal coordination of the borane moiety with the substituent.

Although the results described above are essentially qualitative in nature, some conclusions relating to the intermediates involved can be made. For the vinyl compounds, the introduced borane moiety could coordinate with the alkyl-bearing nitrogen atom in a four-ring or with the carbonyl oxygen atom or terminal nitrogen atom in a six-ring intermediate. In the case of the linear vinyl compounds, the results observed do not distinguish between the probability of a four- or six-ring stabilized intermediate. However, the fact that a yield of greater than 50% of the alkylboronic acid was obtained following the hydroboration of N-cyclohexenylurea would support strongly the likelihood of a six-membered ring intermediate. This is indicated by the fact that borane addition to double bonds is *cis*,[4] and in such a fixed stereochemical structure the formation of a *trans* four-membered ring is not possible. Nevertheless, it should be noted that in the hydroboration of dibutylethylene boronate[8] 1,1-ethanediboronic acid was the main product after hydrolysis. If the stabilization of this monoalkylborane intermediate is due to boron–oxygen interaction only a four-membered ring could be implicated. Such a hypothesis of a four-ring cyclic intermediate would also account for the facile reduction of acrylic ester[6b] by diborane. The $BH_2$ group of the hydroborated ester could polarize the carbonyl group making it susceptible to reduction by a second mole of $BH_3$.

Of the possible six-membered ring intermediates in the stabilization of the monoalkylboranes, the high electronegativity of the carbonyl oxygen atom would make it an attractive donor for reducing the reactivity of the $BH_2$ group as in XXI. Such an assumption would explain the diminishing yields of the boronic acids as the olefinic center is progressively removed from the carbonyl function. In essence a larger, less stable ring would make a smaller contribution to the stabilization of the monoalkylborane and concomitantly, there would be a lower yield of the boronic acid. The results observed parallel those obtained in the hydroboration of ω-unsaturated carboxylic esters.[6b]



XXI

As corroborative evidence for such cyclic products in the case of the vinylureas and -carbamates are the results obtained with the allylamine derivatives. In addition to the introduction of the boronic acid group on the terminal carbon atom, greater than expected yields of the secondary boronic acid isomer were obtained.[6c] A comparison for the borane intermediates of the two isomers shows that the latter compound would have a favored six-ring intermediate in contrast with a seven-ring structure for the former.

In conclusion, it appears that for vinyl- and allylureas and -carbamates, a monoalkylborane is formed which is stabilized as a cyclic entity preventing further hydroboration by this group. This contention is supported by the isolation of substituted alkylboronic acids in good yield.

## Experimental Section[10]

**Materials.** Tetrahydrofuran (THF) was distilled from lithium aluminium hydride. Diborane gas was supplied by Callery Chemical Co., Pittsburgh, Pa. The various ureas and carbamates employed were prepared by the addition of ammonia, ethanol, or benzyl alcohol to the corresponding isocyanate. These isocyanates all were prepared by the method of Hart[11]: **N-vinyl isocyanate**[11] from acrylyl chloride; **N-1-propenyl isocyanate** (not isolated) from crotonyl chloride; **N-1-cyclohexenyl isocyanate,** b.p. 54° (14 mm.) (*Anal.* Calcd. for $C_7H_9NO$: C, 68.28; H, 7.37; N, 11.38. Found: C, 68.47; H, 7.58; N, 11.20.) from cyclohexene-1-carbonyl chloride[12]; **N-*trans*-2-chlorovinyl isocyanate** (not isolated) from *trans*-2-chloroacrylyl chloride;[13] and **1,2-diisocyanatoethylene** (not isolated) from fumaryl chloride.

The ureas employed were: N-vinylurea;[11] **N-1-propenylurea,** m.p. 108–110° (*Anal.* Calcd. for $C_4H_8N_2O$: C, 47.98; H, 8.05; N, 27.99. Found: C, 48.13; H, 8.30; N, 27.80.); **N-1-cyclohexenylurea,** m.p. 132–134° (*Anal.* Calcd. for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.99. Found: C, 60.42; H, 8.88; N, 19.78.); **N-*trans*-2-chlorovinylurea,** m.p. 172–174° (*Anal.* Calcd. for $C_3H_5ClN_2O$: C, 29.89; H, 4.18; Cl, 29.44; N, 23.25. Found: C, 30.05; H, 4.38; Cl, 29.73; N, 23.28.); and ***trans*-1,2-diureidoethylene,** m.p. 213–214° (*Anal.* Calcd. for $C_4H_8N_4O_2 \cdot 0.25H_2O$: C, 32.32; H, 5.76; N, 37.70. Found: C, 32.73; H, 5.91; N, 37.85.).

The carbamates employed were: ethyl-N-vinylcarbamate;[14] ethyl-N-allylcarbamate;[15] **ethyl-N-but-3-enylcarbamate,** b.p. 52–54° (0.15 mm.) (*Anal.* Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.63; H, 9.40; N, 10.04.) from but-3-

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(10) Analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. All melting and boiling points are listed as they were observed. N.m.r. results were obtained using an analytical A-60 Varian spectrometer.

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enylamine[16] and ethyl chloroformate; benzyl-N-vinylcarbamate;[17] and **benzyl-N-allylcarbamate,** b.p. 104–106° (0.3 mm.) (*Anal.* Calcd. for $C_{11}H_{13}NO_2$: C, 69.04; H, 6.85; N, 7.32. Found: C, 69.33; H, 7.07; N, 7.69.).

**General Hydroboration Procedure.** In a 1-l., three-necked flask equipped with a pressure-equalizing, 250-ml. dropping funnel, a thermometer, a magnetic stirring assembly, and a nitrogen purge system was placed a freshly prepared solution of diborane gas (2–3 g. in 400 ml. of dry tetrahydrofuran). This solution was cooled in an ice–acetone bath to 0°. To this mixture a solution of the substituted olefin (0.1 mole) in tetrahydrofuran (150 ml.) was added dropwise over 30–45 min. with continuous stirring. The temperature was maintained at less than 5° during the entire procedure and after the addition, the mixture was stirred for an additional 30 min. Borane/olefin mole ratios of 1/8 gave essentially the same yield of the described boronic acids. Methanol (75 ml.) then was introduced dropwise at such a rate as to keep the temperature less than 10° and to prevent excessive foaming.

In the cases of the ethyl N-vinyl- and N-allylcarbamates this mixture was evaporated directly and distilled under water aspirator pressure to give the dimethyl esters XII and XVIII of the corresponding boronic acids. For N-vinyl- and N-cyclohexenylurea, direct evaporation afforded the dimethyl esters V and IX of the boronic acids as crystalline solids recrystallizable from methanol–ether mixtures. Treatment of any of these boronic esters with water and slow evaporation gave the corresponding boronic acids. The dimethyl esters of the boronic acids derived from benzyl N-vinyl- and N-allylcarbamates were not isolated as such but were converted by water directly to the corresponding boronic acids XV and XIX. These were obtained by evaporation of the aqueous solution and recrystallized from water. No pure dimethyl ester or boronic acid could be obtained from the hydroboration mixture prepared from N-allylurea. The iminodiethanol derivative of XVII was obtained by adding iminodiethanol (0.1 mole) in dimethylformamide (60 ml.) to the residue remaining after evaporation of the reaction mixture.

The hydroboration of ethyl N-but-3-enylcarbamate was conducted as described above. Direct distillation of the reaction mixture afforded a mixture of the **dimethyl esters of 4-(carbethoxyamido)-butylboronic acid** and **1-methyl-3-(carbethoxyamido)propylboronic acid,** b.p. 102–104° (0.15 mm.). *Anal.* Calcd. for $C_9H_2BNO_4$: C, 49.79; H, 9.28; N, 6.45; B, 4.98. Found: C, 50.01; H, 9.48; N, 6.85; B, 4.68.

**Iminodiethanol Derivatives.** The boronic acid (or dimethyl ester) (1–2 g.) was dissolved in dimethylformamide (DMF) (7 ml.); and added to a solution of iminodiethanol (1–2 g.) in the same solvent (5 ml.). Usually the derivative crystallized at once. If not, addition of tetrahydrofuran or tetrahydrofuran–ether mixture effected precipitation. These compounds were recrystallized usually from DMF–THF mixtures.

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# Bicyclo[1.1.0]butane Chemistry. I. The Synthesis and Reactions of 3-Methylbicyclo[1.1.0]butanecarbonitriles

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*Contribution No. 1121 from the Central Research Department, Experimental Station,*
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**Abstract:** The hydrohalogenation–dehydrohalogenation of 3-methylenecyclobutanecarbonitriles provides a facile, high-yield synthesis of 3-methylbicyclo[1.1.0]butanecarbonitriles. The latter react with a broad spectrum of reagents including acids, electron-deficient multiple bonds, nucleophiles, free radicals, and halogens to give cyclobutanes and cyclobutenes. The bicyclobutane ring system is thermally labile leading to a synthesis of substituted butadienes. Catalytic hydrogenation of bicyclobutanes consumes 2 moles of hydrogen leading to open-chain structures. The bicyclobutane ring system is stable to certain transformations of the nitrile group. These reactions are discussed in terms of the scope, conditions, and mechanistic implications.

The report by Wiberg and Ciula[1] of the first authentic[2] bicyclo[1.1.0]butane derivative, ethyl bicyclo[1.1.0]butane-1-carboxylate, has stimulated interest in the synthesis and chemistry of these highly strained structures. Several techniques have been developed for generating bicyclo[1.1.0]butanes including 1,3-dehydrohalogenation,[1,3] intramolecular insertion or addition of a carbene,[4–13] intermolecular addition of carbenes to cyclopropenes or acetylenes,[14–16]

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