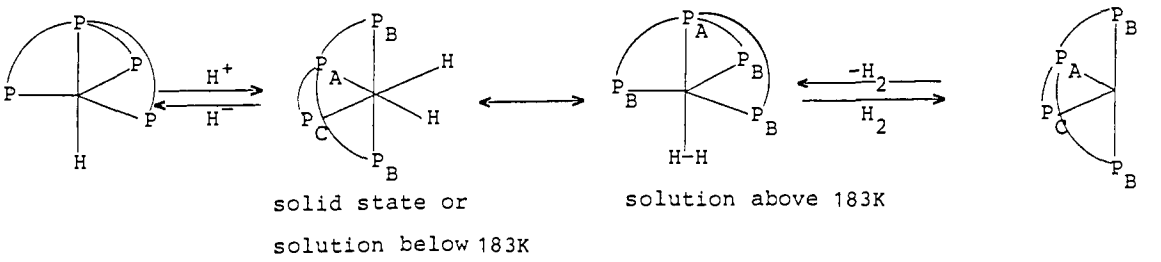


Figure 1. Evolution of the $(PP_3)Rh$ fragment on going from $(PP_3)RhH$ to $(PP_3)Rh^+$.

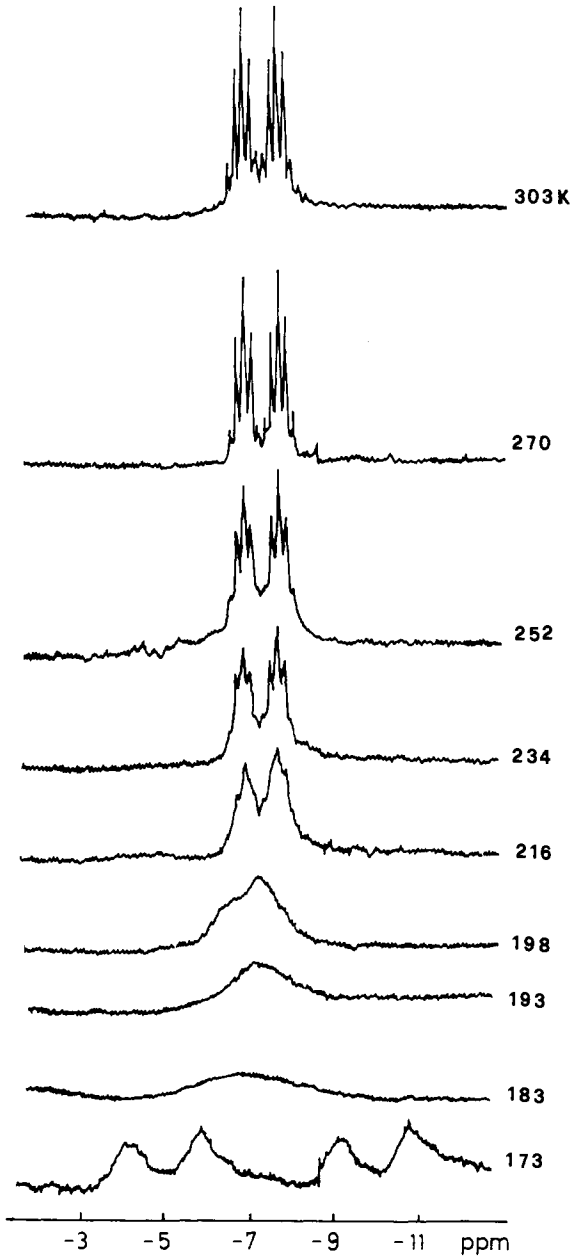


Figure 2. Variable temperature ^1H NMR (TDF, 80 MHz) of $[(PP_3)RhH_2]^+$; Me_4Si reference.

mixture of **2** and **5** in TDF did not provide evidence for crossover products. These results are consistent with previous considerations according to which the simultaneous coordination to two dihydrogen molecules to the same metal center is a condition for the H/D exchange.[1a] Such a process is certainly hampered by the presence of tripodal ligands.

Compound **2** in THF spontaneously loses H_2 at room temperature to give red solutions from which crystals of $[(PP_3)Rh(SO_3CF_3)]$ (**6**) are obtained in 90% yield following the addition of $SO_3CF_3^-$ anion.[10] The conversion of **2** into **6** is completed within 2 h. The compound **6** in turn adds H_2 (1 atm) to reform 2. Finally, **2** quickly exchanges H_2 with C_2H_4 to give $[(PP_3)Rh(C_2H_4)](SO_3CF_3)$[11] (**7**) whose ^{31}P NMR spectrum with an AB_3X spin system closely resembles that of **2**. This result is reasonable because of the analogy between the binding of H_2 and olefins to metals.

It has been previously argued that both steric and electronic factors must be finely "tuned" on a metal fragment to permit the formation of an η^2-H_2 adduct.[1a] The geometric change of the $(PP_3)Rh$ fragment from C_{2v} to C_{3v} symmetry (Figure 1) is accompanied by a certain variation of the fragmental frontier orbitals. Likely the key to understand the mechanism of the present *cis*-dihydride ↔ η^2-dihydrogen interconversion may be found in the orbital control operated by the $(PP_3)Rh$ fragment.

Supplementary Material Available: Analytical data and experimental (80 MHz) and computed ^1H NMR spectrum of $[(PP_3)Rh(HD)](O_2CCF_3)$ (2 pages). Ordering information is given on any current masthead page.

(10) The compound, which is a nonconductor in CH_3CN and $C_2H_5NO_2$, exists in solution as a 1:1 mixture of two isomers most likely due to the triflate ligand (IR 1310 cm^{-1} (s), ν (SO) of coordinated triflate). $^{31}P\{^1H\}$ NMR (CD_3COCD_3, 298 K) AB_2CX system, isomer 1: δ P_A 112.33, δ P_B 52.06, δ P_C 24.70; isomer 2: δ P_A 104.15, δ P_B 52.06, δ P_A 112.33, δ P_B 52.06, δ P_C 24.70; isomer 2: δ P_A 104.15, δ P_B 52.06, δ P_C 16.52 ($J_{P_AP_B}$ = 27.0 Hz, $J_{P_AP_C}$ = 14.2 Hz, $J_{P_BP_C}$ = 34.3 Hz, J_{P_ARh} = 119.7 Hz, J_{P_BRh} = 132.1 Hz, J_{P_CRh} =140.9 Hz). The colorless tetraphenylborate or tetrafluoroborate salts of $[(PP_3)RhH_2]^+$ are indefinitely stable under a dihydrogen atmosphere but, analogously to **2**, lose H_2 under nitrogen to give red solutions which still exhibit, although poorly resolved, ^{31}P NMR AB_2CX spin systems.

(11) $^{31}P\{^1H\}$ NMR (CD_2Cl_2, 298 K) AB_3X system δ P_A 150.28 ($J_{P_AP_B}$ = 22.2 Hz, J_{P_ARh} = 102.0 Hz), δ P_B 55.25 (J_{P_BRh} = 129.4 Hz); ^1H NMR (CD_2Cl_2, 298 K) δ 3.29 (s, C_2H_4, 4 H).

Organoselenium Chemistry.[1] Redox Chemistry of Selenocysteine Model Systems

Hans J. Reich* and Craig P. Jasperse

Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

Received March 30, 1987

Glutathione peroxidase is a mammalian selenoenzyme that catalyzes the reduction of hydroperoxides by glutathione[2] and which represents the principal role played by the essential trace element selenium.[3] Isolation studies have shown that its active

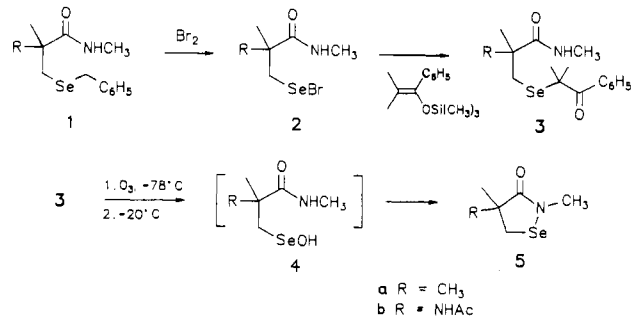
(1) For some previous papers in this sequence, see: (a) Reich, H. J.; Jasperse, C. P.; Renga, J. M. *J. Org. Chem.* **1986**, *51*, 2981. (b) Reich, H. J.; Hoeger, C. A.; Willis, W. W., Jr. *Tetrahedron* **1985**, *41*, 4771. (c) Reich, H. J.; Hoeger, C. A.; Willis, W. W., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 2936. (d) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697. (e) Reich, H. J.; Willis, W. W., Jr.; Wollowitz, S. *Tetrahedron Lett.* **1982**, *23*, 3319. (f) Reich, H. J.; Jasperse, C. P., submitted for publication. (g) Reich, H. J.; Yelm, K. E.; Wollowitz, S. *J. Am. Chem. Soc.* **1983**, *105*, 2503.

(2) Flohe, L.; Loschen, G.; Gunzler, W. A.; Eichele, E. *Hoppe-Seyler's Z. Physiol. Chem.* **1972**, *353*, 987.

(3) (a) Ganther, H. E.; Kraus, R. J. *Meth. Enzymol.* **1984**, *107*, 593. (b) Tappel, A. L. *Curr. Top. Cell. Regul.* **1984**, *24*, 87. (c) Flohe, L. *Curr. Top. Cell. Regul.* **1985**, *27*, 473.

0002-7863/87/1509-5549$01.50/0

Scheme I. Preparation of **5**

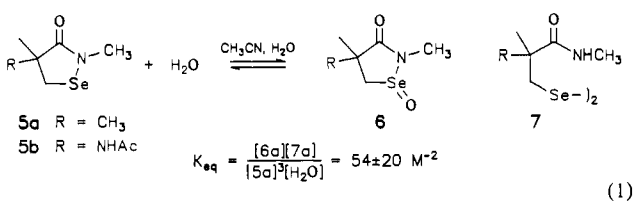


sites contain selenocysteine; a catalytic cycle describing the biological reactivity of the enzyme has been proposed in which selenenic acid is central and in which seleninic acid may be formed when peroxide concentration is high.[3a,b,4] We have developed model systems which suggest that the enzyme in its oxidized form may have a cyclic selenenamide structure.

Because the oxidation of selenocysteine leads to the formation of dehydro derivatives by seleninic acid syn elimination,[1b-d] we chose to investigate α-methyl substituted model systems in which this reaction was prevented. The starting Se–Bzl derivatives **1a** and **1b** (Scheme I) were prepared by alkylation of the appropriate enolate with benzyl bromomethyl selenide.[1a] Conversion to **2** and the selenides **3**[1a] followed by ozonization in chloroform or methylene chloride solution gave the unstable selenoxides, which decomposed at −20 °C. The intermediate selenenic acids **4** were not observed, only the cyclic selenenamides **5**. The same compounds were formed by treatment of the selenenyl bromides **2** with triethylamine. They were reasonably stable even at room temperature but were prone to disproportionation.

These isoselenazolidin-3-ones are a previously undescribed class of heterocycles, although benzoisoselenazolines (e.g., Ebselen) are known.[5] Compounds **5** were characterized by NMR spectroscopy;[6a] cyclization of *N*-methyl amide was visible by ^{1}H NMR because of the *N*-methyl doublet became a singlet and typically moved downfield by ≈0.2 ppm. That the selenium was bonded to nitrogen and not to oxygen was evident from the ^{77}Se NMR shifts of 819 ppm for **5a** and 861 ppm for **5b**[6b] and from the coupling between selenium and the *N*-methyl protons, which at 8 and 6 Hz is more consistent with a three-bond than a four-bond coupling.[7] The chemical formulas were confirmed by mass spectroscopy, and IR spectra and chemical derivatization were in keeping with the assigned structures.

The isoselenazolidin-3-one **5a** equilibrated with the 1-oxoisoselenazolidin-3-one **6a** and the diselenide **7a** (eq 1) under acid catalysis. Figure 1 shows the log/log plot of [**5a**] vs. [**6a**][**7a**]



$$K_{eq} = \frac{[6a][7a]}{[5a]^3[H_2O]} = 54 \pm 20\ M^{-2} \quad (1)$$

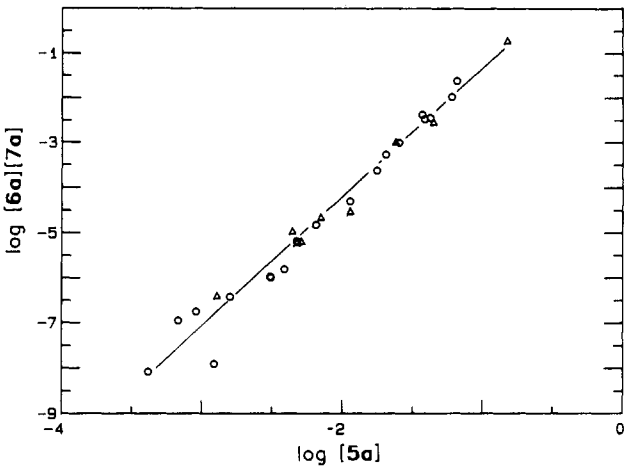


Figure 1. Disproportionation (○) and comproportionation (△) of **5a**, **6a**; and **7a** in 1 M H_2O/CH_3CN at 25 °C.

in aqueous acetonitrile. The slope of the line is 3.0, confirming the inverse cubic dependence of K_{eq} on [**5a**]; K_{eq} was also found to vary inversely with the water concentration as expected. Solutions analyzed by both HPLC and ^{1}H NMR gave consistent results.

The above data constitute the first direct observation of the equilibration of selenium in its intermediate selenenic oxidation state **5a** with its usually more stable higher and lower seleninic **6a** and diselenide **7a** disproportionation products.[1g,8] Although redox equilibria between seleninic acids and diselenides do occur,[1d,9] no detectable amounts of selenenic acids were present at equilibrium. The selenenic acid **4a** was probably an intermediate in the equilibration of **5a** with **6a** and **7a**, but all attempts to hydrolyze **5a** to **4a** failed to give observable amounts of **4a**. This is not surprising, since no alkyl selenenic acids have ever been observed.[1b]

The availability of stable selenenic acid derivatives **5a**,**b** and other members of the redox family allowed us to test the Ganther scheme[3a] for the action of glutathione peroxidase. The following experiments are presented for the model system with R = CH_3 (a series), but similar reactivity was observed for the amino acid derivative R = NHAc (b series).

Oxidation. The reaction of selenol **8a** with *m*-chloroperbenzoic acid or *tert*-butyl hydroperoxide gave first the diselenide **7a** and then the cyclic seleninamide **6a**. Oxidation of the selenenamide **5a** also gave **6a** and was more rapid than oxidation of the diselenide **7a**.

Reduction with Thiols. Reduction of the cyclic seleninamide **6a** with α-toluenethiol or 2-methyl-2-propanethiol under weakly acidic conditions (0.1 equiv of CF_3CO_2H) gave the selenosulfides **9** and **10** and disulfide.

Under weakly basic conditions (0.1 equiv of $(Me_3Si)_2NH$) the same selenosulfides were ultimately formed, but the behavior was more complex. With 2-methyl-2-propanethiol the intermediate thiolseleninate **12** (90%) was detected. It survived in solution for several hours but could not be isolated and was characterized by ^{1}H NMR (which showed diastereotopicity), by ^{77}Se NMR (δ 1089), and by its identity with material prepared by oxidation of selenosulfide **10**. We made the interesting observation that although decomposition of thiolseleninate **12** was acid catalyzed, the rate was independent of 2-methyl-2-propanethiol concentration (t = 3 h with 0, 2, or 10 equiv of thiol).[10] Perhaps the rate-determining step is rearrangement to the selenenic–sulfenic mixed anhydride (RSOSeR′).

(4) Epp, O.; Ladenstein, R.; Wendel, A. *Eur. J. Biochem.* **1983**, *133*, 51.

(5) Lesser, R.; Weiss, R. *Chem. Ber.* **1924**, *57*, 1077. Muller, A.; Cadenas, E.; Graf, P.; Sies, H. *Biochem. Pharmac.* **1984**, *33*, 3235. Wendel, A.; Tiegs, G. *Biochem. Pharmac.* **1986**, *35*, 2115.

(6) (a) ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.30 (s, 6 H), 2.92 (s, $^3J_{SeH}$ = 8.0 Hz, 3 H), 3.50 (s, $^2J_{SeH}$ = 12.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.68, 32.25, 35.93, 43.57, 178.62; IR ($CHCl_3$) 3000, 2930, 1640, 1385, 1360, 1040, 670 cm^{-1}; MS, M$^+$ 193.0007 (calcd. 193.0003). (b) Other selenenamide chemical shifts: $PhC(O)CMe_2SeNMe_2$ δ_{Se} = 994 ppm,[1b,c] $PhSeNEt_2$ δ_{Se} = 769 ppm. For 2-nitro-, 2-carbomethoxy- and 2,4,6-tri-*tert*-butylbenzeneselenenic acids: δ_{Se} = 1066,[1e] 1091,[1c] 1061[1f] ppm.

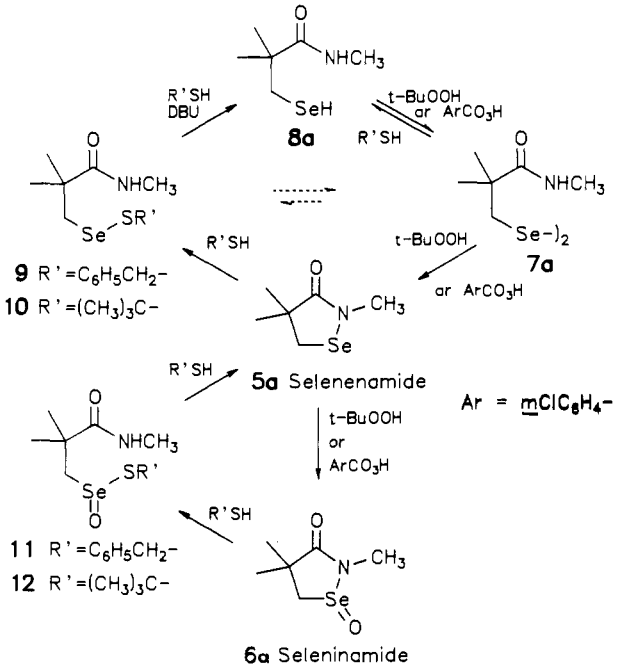
(7) Three-bond $^3J_{SeNCH}$ of 10 Hz[1b] for $PhC(O)CMe_2SeNMe_2$ and 8.8 Hz for 2,4,6-(t-Bu)$_3C_6H_2SeNHCH_2Ph$ have been observed. $^3J_{SeOCH}$ is similar in magnitude.[1c,f]

(8) Gancarz, R. A.; Kice, J. L. *Tetrahedron Lett.* **1981**, *22*, 1661.

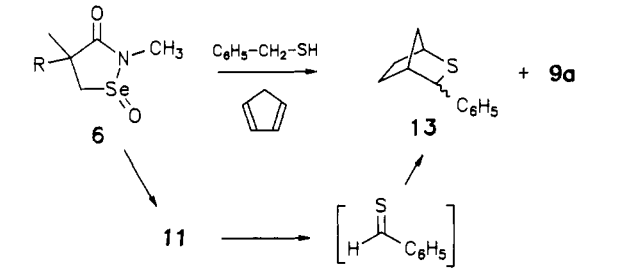
(9) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689. Kuwajima, I.; Shimizu, M.; Urabe, H. *J. Org. Chem.* **1982**, *47*, 837.

(10) This behavior is similar to that observed during the reaction of *t*-BuSH with $PhSeO_2H$ (Kice, J. L.; Lee, T. W. S. *J. Am. Chem. Soc.* **1978**, *100*, 5094.). However, the reaction of thiolseleninate to give selenosulfide was first order in *t*-BuSH.

Scheme II. Redox Chemistry of **5a**



No benzyl thiolseleninate **11** was detected in the reaction of α-toluenethiol with **6a** under basic conditions. The transient



appearance of blue color, however, and the formation of selenosulfide **9** and adduct **13**[11] in high yield when cyclopentadiene was present demonstrated that thiobenzaldehyde was formed, probably by a syn elimination of the thiolseleninate **11**.[12] No selenenamide **5a** was observed, but this was expected since benzyl thiol reacted faster with **5a** than with **6a** under these conditions.

The diselenide **7a** and selenosulfide **9** did not react with α-toluenethiol under neutral conditions but with excess DBU each gave the selenolate **8a** and disulfide. ^{1}H NMR analysis of such mixtures was complicated by the rapid equilibration of selenolate **8a**$^-$ with diselenide **7a** such that only a single set of resonances was observed for the selenium-containing fragment. The selenolate was quantitatively trapped in situ by benzyl bromide to give the benzyl selenide or by a rapid quench with trifluoroacetic acid, giving selenol **8a** in yields as high as 85% when a tenfold excess of thiol was used.

Scheme II summarizes the redox results. Inspection of the scheme reveals that most of the features of the proposed glutathione peroxidase mechanism have been reproduced, with the selenenamide **5a** replacing the selenenic acid. The principle exception is that oxidation of selenol did not lead to **5a** but rather to the diselenide **7a**.

Acknowledgment. We thank the National Institutes of Health-NIADDK and the Wisconsin Alumni Research Foundation for support of this work.

(11) Vedejs, E.; Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556.

(12) Syn eliminations of a selenolseleninate[1b] and thiolsulfinates (Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929. Baldwin, J. E.; Lopez, R. C. G. *Tetrahedron* **1983**, *39*, 1487) have been observed.

Highly Enantioselective Borane Reduction of Ketones Catalyzed by Chiral Oxazaborolidines. Mechanism and Synthetic Implications

E. J. Corey,* Raman K. Bakshi, and Saizo Shibata

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received May 11, 1987

In recent years there has been a flood of papers describing research on the enantioselective reduction of ketones by a wide variety of reagents made by mixing aluminum or boron hydrides and various chiral diols or amino alcohols.[1] Although a number of systems have been described which provide useful enantioselectivity, our knowledge of reagent structure, scope, and mode of reduction has remained at a primitive level, limiting both application and further development. Among the most interesting enantioselective ketone reductions have been those reported by Itsuno and his group which employ mixtures of borane (2–3 molar equiv) in tetrahydrofuran (THF) and a chiral vicinal amino alcohol (1 equiv), (*S*)-2-amino-3-methyl-1,1,-diphenylbutan-1-ol (**1**) and the corresponding derivative from (*S*)-leucine thus far being the most effective (ca. 95% ee of (*R*)-1-phenylethanol from acetophenone).[2] Typically a 2.5:1 mixture of borane and the amino alcohol in THF is allowed to react at 0 °C for several hours (hydrogen evolution) giving a reducing mixture to which the ketone is added for reduction at 0–30 °C. Reduction of ketones with this reagent is faster than that with borane in THF at the same temperature.

We have found that a fast reaction occurs between amino alcohol **1** and 2 equiv of borane in THF at 35 °C to give 2 equiv of hydrogen gas and the oxazaborolidine **2**. Removal of excess borane and solvent in vacuo and two sublimations of the solid residue at 105–130 °C and 0.05 Torr afforded colorless crystals of **2**, mp 105–110 °C, electron impact mass spectrum (EIMS), M^+ 265.16365 (calcd. 265.16379).

The ^{1}H NMR spectrum of **2** (250 MHz in C_6D_6, δ) showed the expected peaks due to ligand [6.93–7.70 (m, 10 H, phenyl), 3.98 (dd, J = 2.9 Hz, ca. 1.5 Hz, 1 H, C–CH–N), 3.24 (br s, 1 H, NH), 1.66 (m, 1 H, $CHMe_2$), 0.535 (d, J = 6.9 Hz, 3 H, CH_3), and 0.42 (d, J = 6.5 Hz, 3 H, CH_3)], and the ^{11}B NMR spectrum (in THF) showed a single broadened peak at +28.1 ppm (downfield) from BF_3·Et_2O (internal capillary), clearly due to B–H since it narrowed upon broad band ^{1}H decoupling.[3] Although the B–H proton in **2** was not apparent in the ^{1}H NMR spectrum due to broadening,[4] the infrared spectrum (in THF) showed a characteristic B–H stretching band at 2563 cm^{-1} as well as N–H stretching at 3400 cm.$^{-1}$ ^{11}B NMR spectral studies as a function of concentration revealed that **2** is monomeric in 0.05–0.2 M solution. Solutions of **2** alone in THF did not reduce ketones, e.g., acetophenone, even after several hours at 23 °C. However, mixtures of **2** and BH_3·THF (0.6–2.0 mol equiv) effect complete reduction of acetophenone in less than 1 min at 23 °C with rates comparable to the Itsuno mixtures. Under the same conditions

(1) For reviews, see: (a) ApSimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157–5254. (b) Haubenstock, H. *Topics Stereochem.* **1983**, *14*, 231–300. (c) Mukaiyama, T.; Asami, M. In *Topics in Current Chemistry, No. 127, Organic Chemistry*; Springer-Verlag: Berlin, 1985; pp 133–167.

(2) See: (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469–470. (b) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555–557. (c) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans 1* **1985**, 2039–2044. (d) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2615–2619. (e) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395–396.

(3) The observed ^{11}B NMR chemical shift is consistent with structure **2**, see: (a) Eaton, G. R.; Lipscomb, W. N., *NMR Studies of Boron Hydrides and Related Compounds*; W. A. Benjamin: New York, 1969. (b) Nöth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Springer-Verlag: Berlin, 1978.

(4) See: Leach, J. B.; Ungermann, C. B.; Onak, T. P. *J. Magn. Reson.* **1972**, *6*, 74–83.

0002-7863/87/1509-5551$01.50/0