ethanol, and ether), and 1.5 mL of acetic acid was stirred at room temperature for 24 h and filtered; the filter cake was washed with 5 mL of acetic acid. The filtrate was concentrated, 5 mL of 2 N NaOH was added, and the amine product isolated by $CHCl_3$ extraction was dried over Na_2SO_4. Concentration afforded 67 mg (91%) of pure **9**: mp (HBr salt) 240–241 °C dec; IR (film) 3380, 1730, 1260, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4 (apparent s, Ph), 6.3–5.5 (m, CH=CH), 3.6–4.4 (m, $CHNH_2$ and nonequivalent CH_2CH_3), 1.10 (t, J = 7 Hz, CH_3), 0.6–1.1 (broad s, NH_2); mass spectrum (isobutane CI), m/z 246 (100), 229 (31), 155 (7).

Ethyl *trans*-2-(Dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylate (Tilidine) (2). The general procedure of Borch was followed.[10] Sodium cyanoborohydride (45 mg, 0.72 mmol) was added in one portion to a stirred solution of **9** (110 mg, 0.45 mmol), formaldehyde (0.18 mL, 37% aqueous solution), and 1.4 mL of acetonitrile at room temperature. After being stirred at room temperature for 12 h, the solution was neutralized by adding acetic acid dropwise and concentrated, 5 mL of 2 N KOH was added, and the mixture was extracted (3 × 10 mL) with ether. The ether extracts were washed with 5 mL of 0.5 N KOH and extracted (3 × 5 mL) with 1 N HCl. The combined acid extracts were basified by adding solid KOH, extracted (3 × 10 mL) with chloroform, and dried (K_2CO_3). Concentration gave 86 mg (70%) of **2**: a colorless liquid which was pure by TLC and ^{13}C NMR; mp (HCl salt) 158.5–159 °C (lit.[5a] mp 159 °C).

Crystallography. Single crystals were prepared by slow crystallization from hexane–ethyl acetate. A small crystal measuring approximately 0.5 mm × 0.2 mm × 0.6 mm was cut from a larger one and mounted for data collection. The crystal was found to belong to the orthorhombic system with unit cell dimensions at 23 °C: a = 20.000 (4), b = 11.092 (2), c = 9.231 (1) Å. Systematic absences indicated that the space group was either $P2_1ab$ or $Pmab$. Intensity statistics suggested a noncentrosymmetric structure and thus indicated the space group $P2_1ab$. The measured density, 1.23 g/cm^3, agrees favorably with the calculated value of 1.22 g/cm^3 for Z = 4 molecules per unit cell. Three-dimensional intensity data were collected on a Syntex $P2_1$ automated diffractometer, using monochromatized Mo Kα radiation (λ = 0.70930 Å). The θ–2θ scan technique was used to measure the intensities of 1867 independent reflections within the range $0° < 2\theta < 50°$.[14] Of these, 1295 had $F^2 > 3\sigma(F^2)$ and were used in subsequent calculations.

The structure was solved, with considerable difficulty, by direct methods, using the MULTAN 77 system of programs.[15] The central atoms, excluding hydrogens, were anisotropically refined, using full-matrix least-squares methods. The phenyl substituents were treated as groups[16] with individual isotropic temperature factors for the carbon atoms. Phenyl hydrogen atoms were included in the groups with fixed thermal parameters at 6.5 $Å^2$; nongroup hydrogens were included at their idealized positions with fixed isotropic temperature factors. The final unweighted and weighted R values were 0.062 and 0.075, respectively. A final difference map showed no significant residual features.

Acknowledgment. This work was generously supported by a grant from the National Institutes of Health (NS-12389).

Registry No. **2**, 51931-66-9; **2**·HCl, 35481-00-6; **3**, 20380-56-7; **4**, 71616-72-3; **5**, 71616-73-4; **6**, 71616-74-5; **7**, 71616-75-6; **8**, 71616-76-7; **9**, 71656-78-5; **9**·HBr, 71656-79-6; *trans*-2,4-pentadienoic acid, 21651-12-7; 2,2,2-trichloroethanol, 115-20-8; ethyl atropate, 22286-82-4.

Supplementary Material Available: Tables I–VII of atomic positional and thermal parameters, bond distances, and bond angles (8 pages). Ordering information is given on any current masthead page.

(14) General procedures for data collection and processing have been given in Sams, D. B.; Doedens, R. J. *Inorg. Chem.* **1979**, *18*, 153. Details specific to the current analysis include: scan rate, 2.0 deg/min in 2θ; scan range, −0.9 deg from the Kα_1 peak to +0.9 deg from the Kα_2 peak; stationary background counts at each end of the scan, each for half of the scan time; p factor in the calculation of standard deviations, 0.05.

(15) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P., MULTAN 77, University of York, York, England, 1977.

(16) Doedens, R. J. In "Crystallographic Computing"; Ahmed, F. R., Ed.; Munksgaard: Copenhagen, 1970; pp 198–200.

Stereochemistry of the Protonolysis of Organoboranes

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The hydroboration of alkenes coupled with the protonolysis of the resultant organoboranes affords a convenient alternative to catalytic hydrogenation.[2] This sequence is particularly useful in instances in which sulfur, halogens, or nitrogen substituents are present in the alkene.

The protonolysis reaction is thought to occur with retention of configuration at the carbon attached to boron. This belief is based primarily on the facts that deuteriolysis of chiral dibutyl 1-phenylethylboronate produces chiral α-deuterioethylbenzene[3] and that the hydroboration–deuteriolysis of norbornene yields 2-*exo*-deuterionorbornane.[4] Unfortunately, the absolute configuration of the deuterioethylbenzene was not determined and consequently the question of retention vs. inversion was not decided; in addition, the use of rigid bicyclic systems in stereochemical investigations is subject to uncertainties.[5] We felt that the protonolysis of organoboranes was of sufficient importance to warrant the unambiguous determination of its stereochemistry. Nuclear magnetic resonance spectroscopy was chosen as the appropriate analytical method due to its proven utility in stereochemical investigations.[6-8]

We recently demonstrated that the hydroboration reaction proceeds via the syn addition of the boron–hydrogen moiety to an alkene.[6] Knowledge of the stereochemistry of the hydroboration reaction permits a straightforward determination of the stereochemistry of the protonolysis reaction. Thus, retention of configuration during the protonolysis of an organoborane would produce an overall syn hydrogenation of an alkene which has been submitted to the hydroboration–protonolysis sequence. Inversion of configuration during the protonolysis reaction would result in overall anti hydrogenation.

Results and Discussion

(*Z*)- and (*E*)-1-phenyl-3,3-dimethyl-1-butenes-*1,2-d_2* (**1** and **2**, respectively) were hydroborated and the intermediate organoboranes were protonolyzed. An overall syn hydrogenation (retention of configuration during protonolysis) would produce *erythro*- and *threo*-1-phenyl-3,3-dimethylbutane-*1,2-d_2* (**3** and **4**), respectively. An overall anti

(1) (a) University of Tennessee. (b) Tulane University.

(2) H. C. Brown, "Organic Synthesis via Boranes", Wiley, New York, 1975.

(3) A. C. Davies and B. P. Roberts, *J. Chem. Soc. C*, **27**, 1474 (1968).

(4) H. C. Brown and K. J. Murray, *J. Org. Chem.*, **26**, 631 (1961).

(5) Rigid bicyclic systems possess stereochemical biases which can affect the stereochemistry of the product. As an example, Larock reports that the mercuration of tri-*exo*-norbornylborane produces 93% of the *exo*-mercurial product [R. C. Larock and H. C. Brown, *J. Organomet. Chem.*, **26**, 35 (1971)]. However, Gielen reports that mercuration of an (*erythro*-3,3-dimethyl-1-butyl-*1,2-d_2*)borane proceeds with inversion of configuration [M. Gielen and R. Fosty, *Bull. Soc. Chim. Belg.*, **83**, 333 (1974)].

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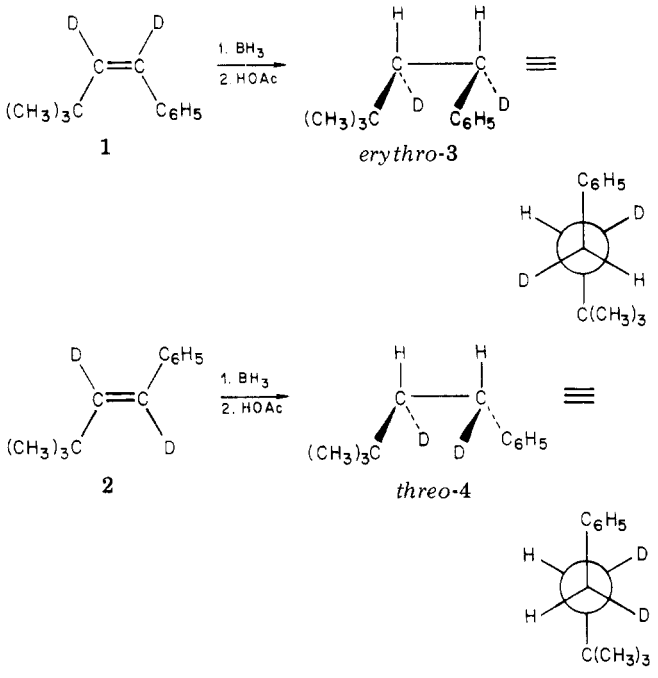

hydrogenation (inversion of configuration during protonolysis) would produce the opposite stereochemical results.

The steric bulk of the *tert*-butyl and the phenyl group ensures that the anticonformer of each product is predominantly, if not exclusively,[9] populated. The experimental results provide compelling evidence that an overall syn hydrogenation is achieved via the hydroboration–protonolysis sequence.[10] Consequently, the protonolysis reaction occurs with retention of configuration at the carbon originally attached to boron.

The ^{2}H-decoupled, ^{1}H NMR spectra clearly demonstrate that *erythro*-**3** (^3J_H = 12.5 Hz) is produced from **1** and *threo*-**4** (^3J_H = 5.0 Hz) is produced from **2** by the hydroboration–protonolysis sequence. The low-field regions of the ^{1}H NMR spectra of the products are presented in Figure 1.

It must be concluded that the protonolysis of organoboranes proceeds with retention of configuration in accordance with Brown's original postulation.

Experimental Section

The hydroboration reactions were carried out in flame-dried, nitrogen-purged glassware. Diglyme (Ansul) was distilled from calcium hydride prior to use. All other solvents were used as received. Ethyl bromide (Fisher), copper(I) chloride (Alfa), iodobenzene (Aldrich), lithium aluminum deuteride (Merck Sharp and Dohme), cyclohexene (Eastman), acetic acid-d_4 (Aldrich), and iodine (Fisher) were used as received.

Routine ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer. ^{2}H-decoupled proton and ^{1}H-decoupled deuterium NMR spectra were recorded on a Bruker HX-90 spectrometer at 90 and 13.8 MHz, respectively. Chemical shifts for the ^{1}H NMR spectra are reported in ppm relative to internal Me_4Si. Chemical shifts for the ^{2}H NMR spectra, which were assigned relative to internal benzene-d_6, are normalized to Me_4Si.

1-Phenyl-3,3-dimethyl-1-butyne. Ethylmagnesium bromide (510 mmol, 67.5 g) in ethyl ether was prepared in a dry, three-necked flask equipped with a pressure-equalizing dropping funnel, reflux condenser, and magnetic stirring bar. 3,3-Dimethyl-1-butyne[11] was placed in the dropping funnel and added over a 2-h period to the Grignard solution cooled to 0 °C (ice bath). The mixture was left to stir overnight to ensure complete conversion to the acetylenide salt. The ethyl ether solvent was removed by distillation, leaving a gray, powdery solid. Pyridine (400 mL) was added as solvent, followed by copper(I) chloride (500 mmol, 50.0 g) and iodobenzene (500 mmol, 56.0 mL). The reaction mixture was refluxed overnight.

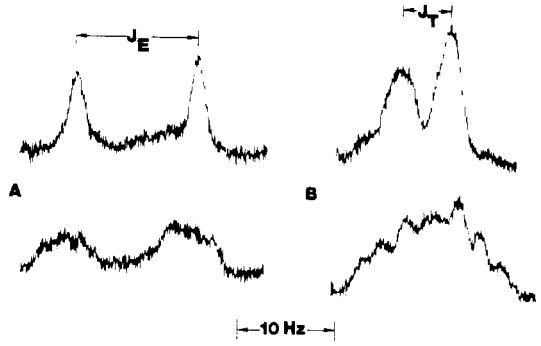

Figure 1. Proton spectrum (90 MHz) of *erythro*-1-phenyl-3,3-dimethylbutane-*1,2*-d_2 (**3**): (A, upper) ^{2}H-decoupled, (A, lower) normal (undecoupled) spectrum. Proton spectrum (90 MHz) of *threo*-1-phenyl-3,3-dimethylbutane-*1,2*-d_2 (**4**): (B, upper) ^{2}H-decoupled, (B, lower) normal (undecoupled) spectrum.

The contents of the reaction flask were poured into a 1-L separatory funnel containing 300 mL of water. This mixture was extracted with four 100-mL portions of ether. The combined ether layers were washed with four 100-mL portions of 2 N aqueous HCl and two 100-mL portions of aqueous $NaHCO_3$ (saturated). The ether layer was separated, dried over anhydrous magnesium sulfate, and filtered, and the ether was removed and the product distilled: bp 68 °C (7.2 mm) [lit.[12] bp 84 °C (10 mmHg)]; ^{1}H NMR (CCl_4) δ 7.26 (m, 5), 1.36 (s, 9); IR (CCl_4) 3100 (vs), 2900 (vs), 2260 (m) cm^{-1}.

(*Z*)-1-Phenyl-3,3-dimethyl-1-butene-*1,2*-d_2. Bis(2-deuteriocyclohexyl)borane-*B*-d_1[6] (65 mmol) in 100 mL of diethyl ether was placed in a dry, nitrogen-flushed, 250-mL, three-necked flask equipped with a pressure-equalizing dropping funnel, reflux condenser, magnetic stirring bar, and gas exit tube. 1-Phenyl-3,3-dimethyl-1-butyne (60 mmol, 9.48 g) was placed in the dropping funnel and added over a 1-h period. The reaction mixture was heated (oil bath) to reflux for 3 h to ensure complete hydroboration. Acetic acid-d_4 (200 mmol, 12.1 mL) was placed in the dropping funnel and added dropwise. The solution was refluxed overnight. The ether solution was extracted with four 100-mL portions of water and 100 mL of saturated aqueous $NaHCO_3$ and dried over anhydrous magnesium sulfate. The product was obtained by fractional distillation (6.8 g, 70%): bp 46–48 °C (1 mmHg); ^{1}H NMR (neat) δ 7.1 (s, 5), 0.95 (s, 9).[13] The ^{1}H-decoupled, ^{2}H NMR spectrum exhibits two signals at δ 6.29 (br s, 1) and 5.49 (br s, 1).

(*E*)-1-Phenyl-3,3-dimethyl-1-butene-*1,2*-d_2. The *Z* isomer (42 mmol, 8.0 mL) was placed into a 50-mL flask fitted with a reflux condenser and magnetic stirring bar and containing dioxane (30 mL). Iodine (6.3 mmol, 0.8 g) was added, and the mixture was heated to reflux. After a 48-h period, ^{1}H NMR analysis revealed 97% of the *E* isomer in the mixture. The product was recovered by fractional distillation through a 6-in. Vigreux column: bp 52–54 °C (1 mmHg); ^{1}H NMR (CCl_4) δ 7.17 (m, 5), 1.09 (s, 9).[13] The ^{1}H-decoupled, ^{2}H NMR spectrum exhibited one broad singlet at δ 6.15.

***erythro*-1-Phenyl-3,3-dimethylbutane-*1,2*-d_2.** The *Z* alkene (1; 4.2 mmol, 0.69 g) and diglyme (10 mL) were placed in a dry, nitrogen-flushed, 50-mL flask fitted with a septum inlet, reflux condenser, magnetic stirring bar, and gas exit tube. The solution was cooled to 0 °C, and BH_3·THF (2.1 mmol, 1.19 mL) was added via syringe (10 min). The reaction mixture was allowed to warm to room temperature and was subsequently heated to 50 °C for

(9) G. W. Kabalka and J. Jacobus, *J. Org. Chem.*, in press.

(10) It is interesting to note that the products obtained via the hydroboration–protonolysis were purer than the reference samples obtained via hydrogenation of (*Z*)- and (*E*)-1-phenyl-3,3-dimethyl-1-butene-*1,2*-d_2 over palladium on charcoal. Presumably hydrogen–deuterium exchange occurred during the hydrogenation reactions.

(11) J. J. Eisch and M. W. Foxton, *J. Org. Chem.*, **36**, 3520 (1971).

(12) B. S. Kupin and A. A. Petrov, *Chem. Abstr.*, **57**, 2126a (1962).

(13) H. Kristinsson and G. W. Griffin, *J. Am. Chem. Soc.*, **88**, 378 (1966).

1 h to ensure complete hydroboration. Acetic acid (20 mmol, 2.0 mL) was added in one portion and the temperature maintained at 110 °C for 3 days. The reaction solution was cooled and transferred to a 250-mL separatory funnel. The flask was rinsed with two 25-mL portions of pentane. The combined organic layers were extracted with four 50-mL portions of cold water and with one 50-mL portion of aqueous $NaHCO_3$ (saturated). The pentane layer was separated and dried over anhydrous magnesium sulfate. The product was isolated by fractional distillation (3.5 g, 50%): bp 44–46 °C (1 mmHg); ^{2}H-decoupled ^{1}H NMR δ 7.07 (s, 5), 2.53 (d, 1, $J_{H^aH^b}$ = 12.5 Hz), 1.53 (d, 1, $J_{H^aH^b}$ = 12.5 Hz), 0.93 (s, 9).

***threo*-1-Phenyl-3,3-dimethylbutane-*1,2*-d_2.** The *E* alkene (**2**; 8.4 mmol, 1.38 g) was hydroborated and protonolyzed as described for the *Z* isomer. The product was isolated by distillation (0.62 g, 45%): bp 52–54 °C (1 mmHg); ^{2}H-decoupled ^{1}H NMR δ 7.07 (s, 5), 2.53 (d, 1, $J_{H^aH^b}$ = 5.0 Hz), 1.53 (d, 1, $J_{H^aH^b}$ = 5.0 Hz), 0.93 (s, 9).

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Registry No. 1, 71486-30-1; **2**, 71486-31-2; *erythro*-**3**, 71486-32-3; *threo*-**4**, 71486-33-4; 1-phenyl-3,3-dimethyl-1-butyne, 4250-82-2; 3,3-dimethyl-1-butyne, 917-92-0; iodobenzene, 591-50-4.

Lanthanoids in Organic Synthesis. 4.[1] Selective Ketalization and Reduction of Carbonyl Groups

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The transformation of aldehydes and ketones to cyclic or noncyclic ketals is one of the easiest and most efficient protective methods for carbonyl groups against nucleophilic reagents.[2] This reaction is usually performed in the presence of various acidic catalysts. During the synthesis of complex molecules, a situation may occur in which one carbonyl group must be selectively transformed in the presence of another. This desired result can often be obtained by blocking a given carbonyl group, so that it is important from a synthetic viewpoint to know specific ketalization processes and catalysts.

We recently reported the efficient ketal formation from aldehydes under mild conditions in the presence of lanthanoid ions.[1] As the yields are excellent and the reaction is very easy to accomplish, it was of interest to further investigate the ketalization process with ketones and bifunctional molecules. The results reported in this note emphasize the sharp contrast between aldehyde and ketone ketalization when rare-earth chlorides are used as catalysts.

Aromatic ketones (e.g., acetophenone, benzophenone, and benzosuberone) and α-enones[3] remain unaffected under the reaction conditions. The reactivity of aliphatic and alicyclic ketones, however, is less straightforward for reasons which still remain obscure. Whereas cyclohexanone and its 4-*tert*-butyl analogue yield the corresponding ketal quantitatively in the presence of $NdCl_3$, other ketones gives unexpected results with various lanthanoid ions. Attempts to isolate the ketal or to determine its concentration in the reaction mixture frequently gave substantially different results according to the analytical method used;[4] these discrepancies remain unexplained. Instead of ketals, hemiketals may be involved, but it has not been possible to obtain direct evidence for such intermediates.

Irrespective of the actual carbonyl protecting species, the preceding results implied that selective ketalization of aldehydes in the presence of ketones would thus be possible in many cases. Addition of excess $NaBH_4$ to the same reaction mixture should result in the reduction of the free keto group. Deprotection during workup would then afford secondary alcohols and aldehydes (or hydroxyaldehydes). In fact, this is the case, and the net result is that our procedure allows a one-pot specific reduction of a keto group in the presence of an aldehyde.[5] A satisfactory selectivity can thus be obtained as shown in Table I. For best results, the proper choice of catalyst is important. It was previously observed that the ketal yield increases with the atomic number of the rare-earth ion.[1] For many aldehydes, including aromatic aldehydes, and hindered ketones, heavier lanthanoids can be used suc-

Table I. Reduction of Ketones in the Presence of Aldehydes[a]

entry	initial mixture or compd	ketalization catalyst	recovered starting matl, %	reduction prod, %
1	cyclohexanecarboxaldehyde	$NdCl_3$	70	30
	cyclododecanone		8	92
2	cyclohexanecarboxaldehyde	$CeCl_3$	48	52
	benzyl methyl ketone		56	44
3	**1**	$ErCl_3$		70[b] (**2**)
4	**5**	$ErCl_3$		76[c] (**6**)
5	benzaldehyde	$ErCl_3$	93	7
	cycloheptanone		17	83
6	benzaldehyde	$CeCl_3$	83	17
	5-nonanone		16	84
7	benzaldehyde	$ErCl_3$	95	5
	2-cyclohexenone		18	82
8	*p*-anisaldehyde	$ErCl_3$	98	2
	acetophenone		20	80

[a] Yields are calculated from the VPC analysis of the crude mixture. For compounds **2** and **6**, the figures are isolated yields of purified product. [b] One stereoisomer could be detected by NMR in the presence of shift reagents. The absolute configuration of the secondary alcohol function was determined by Horeau's method.[12] [c] 1:1 mixture of the epimeric alcohols.

(1) Previous paper in this series: J. L. Luche and A. L. Gemal, *J. Chem. Soc., Chem. Commun.*, 976 (1978). Contribution No. 42 from the Laboratoire de Chimie Organique, CERMO. For No. 41 see: A. E. Greene and J. P. Deprès, submitted for publication.

(2) For example see: E. Schmitz and I. Eichhorn, *Chem. Ether Linkage*, 309 (1967); Y. Ogata and A. Kawasaki, *Chem. Carbonyl Group*, **2**, 1 (1970); H. J. E. Lowenthal in "Protective Groups in Organic Chemistry", J. F. W. McOmie, Ed., Plenum Press, London, 1973, p 323.

(3) J. L. Luche, *J. Am. Chem. Soc.*, **100**, 2226 (1978); J. L. Luche, L. Rodriguez-Hahn, and P. Crabbé, *J. Chem. Soc., Chem Commun.*, 601 (1978).

(4) As an example, camphor (2 mmol) was submitted to ketalization conditions in the presence of erbium chloride. The resulting solution was separated into two parts. One was treated as described for the isolation of the ketal (see Experimental Section). NMR analysis showed that the initial material was quantitatively recovered. The other half was treated with excess $NaBH_4$ (2–10 equiv), and then aqueous HCl was added (pH 3). After the usual workup, the crude mixture was analyzed by VPC and shown to contain 80% of initial material and only 20% of the reduction products (borneol and isoborneol). Similar behavior was observed with other ketones such as 2-octanone, 2-methylcyclohexanone, 5-nonanone.

(5) For another process with a similar selectivity but with different scope and mechanism see: J. L. Luche and A. L. Gemal *J. Am. Chem. Soc.*, in press.

0022-3263/79/1944-4187$01.00/0