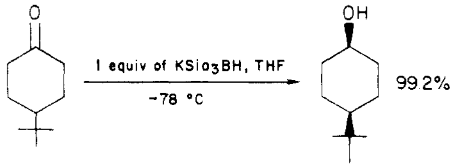
regarded as an inert component; however, it may be readily removed by addition of an equivalent amount of trisiamylborane (eq 2) or another hydride acceptor such as *n*-octyl chloride. The analysis of the solution for K^+:B:H^- indicated it to be essentially 1:1:1. The reagent appears to be quite stable and appears to reduce cyclic ketones with exceptional stereoselectivity, comparable to that of the lithium analogue[5] (eq 6).



(6)

Attempts were made to catalyze the reaction with trimethoxyborane as well. Initially (see Figure 1 and Table I) the reaction appeared to proceed even more readily than with **4** as the catalyst; however, reaction ceased with only 40% of **4** converted to **6**. This apparently reflects destruction of the intermediate **1a** (R = Me) via disproportionation to potassium tetramethoxyborate (stable to KH) and potassium borohydride (insoluble in THF, not observed to transfer hydride to trialkylboranes). Such disproportionation has been reported to be facile and is the basis of the usual preparation of sodium borohydride from trimethoxyborane and sodium hydride.[9]

The curves for triisopropoxyborane catalysis in Figure 1 present a puzzle. The shape of the curve in the figure for 5 mol % triisopropoxyborane clearly shows a marked decrease in rate as the reaction proceeds. Transfer of hydride from **3** to **4** is very fast and quantitative under these conditions. Consequently, we would expect that the observed curve reflects the rate of reaction of **5** with KH(s). However, the latter is present in 50% excess; thus the reaction curve must reflect either a marked decrease in surface area as smaller particles are consumed or some progressive "poisoning" of the KH surface as the reaction proceeds. Moreover, the ratio of observed reaction times (ca. 25:1) with 5 mol % and 20 mol % triisopropoxyborane is much longer than would be expected a priori from the relative amounts of catalyst. This suggests the presence of an impurity which reacts with a fixed amount of the **5** (or **3**), thereby increasing the actual ratio of active catalyst in the two experiments. This is consistent with the possibility that the trialkoxyborane functions to remove a surface contaminant from the KH (as well as serving as a hydride carrier); the reaction with the suggested surface contaminant, if irreversible, would provide the mechanism for loss of catalyst. The importance of this explanation lies in the possibility that, with careful control of reagents, it may be possible to effect the catalysis with only traces of the trialkoxyborane.

The graph shown for trimethoxyborane catalysis in the figure, as the other graphs, was corrected for the maximum amount of trialkoxyborohydride which can be formed. Due to the probably disproportionation and precipitation of hydride derived from trimethoxyborane, this graph could be up to 5% low; this does not affect the conclusions.

In summary, triisopropoxyborane serves as an efficient catalyst for reaction of KH with trisiamylborane, providing the first route to potassium trisiamylborohydride nearly free of other boron species. The procedure is, in all probability, applicable to reaction of other highly hindered trialkyboranes.

Experimental Section

General Considerations. Procedures for the preparation of trialkyboranes, their reactions with KH, and relevant analysis have been published elsewhere in detail.[3,4,10,11] For the catalytic studies purified trialkoxyborane was added to a suspension of KH (50% excess) in THF with stirring under nitrogen. At intervals stirring was stopped and samples of the clear solution were removed with a hypodermic syringe and analyzed for active hydride content by hydrogen gas evolution upon hydrolysis.[10] This analysis gives the total soluble hydride in solution, from both **3** and **6**. The values in the table reflect total hydride found; the graphs in the figure have been corrected for the hydride due to the catalyst. In the case of trimethoxyborane, disproportionation of the trimethoxyborohydride and subsequent precipitation of the tetrahydridoborate (see text) removes from solution the hydride due to catalyst; therefore, in this case, the hydride analyses are assumed to be entirely due to trisiamylborohydride. The maximum discrepancy this could entail in 0.05/0.40 or 12.5%.

Reduction of 4-*tert*-butylcyclohexanone, and GLPC analysis of the products, was carried out according to procedures published for reductions with the lithium analogue.[5]

Potassium Trisiamylborohydride (6). A uniform oil dispersion of potassium hydride (3.0 g net KH, 75 mmol) was transferred under nitrogen to a dry 100-mL round-bottomed flask with the aid of a hypodermic syringe fitted with a 16-gauge needle. The flask was fitted with a poly-TFE covered magnetic stirring bar and an injection port closed by a small rubber septum. The oil carrier was removed by three successive washes of ca. 50 mL of pentane (dried overnight over molecular sieves); residual pentane was removed in a stream of nitrogen. The pure KH was dispersed a 1.0 M solution of trisiamylborane in the THF (50 mL, 50.0 mmol), previously prepared.[11] Triisopropoxyborane (0.58 mL, 2.5 mmol purified by distillation from sodium) was injected to the mixture with a syringe. At intervals stirring was stopped and a 2.0-mL sample of the clear supernatant liquid was withdrawn with an oven-dried syringe and analyzed by hydrolysis with a 1:1:1 mixture of THF:glycerine:aqueous HCl (0.10 N). Hydride content was determined by measurement of the evolved hydrogen. After 24 h the hydride content of the solution was constant at 1.03–1.05 M, indicating a quantitative conversion to **6** (+ca. 5% **4**): IR (THF) 2040 cm^{-1}, B–H stretch; ^{11}B NMR (THF, external BF_3:Et_2O = 0δ), δ = −11.6 and −13.8, J_{B-H} = 75 Hz, two pairs of doublets due to diasteriomers, partially superimposed.

Registry No. **2** (X = MeO), 121-43-7; **4b**, 32327-52-9; **5**, 5419-55-6; **6**, 67966-25-0; KH, 7693-26-7.

---

(10) Brown, C. A. *Inorg. Synth.* **1977**, *17*, 26.

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

Meerwein-Ponndorf-Verley Type Reduction of Ketones and Oppenauer Type Oxidation of Alcohols under the Influence of Cp_2ZrH_2

Yasutaka Ishii,* Tatsuya Nakano, Akihiro Inada,
Yoshitaka Kishigami, Katsunori Sakurai, and
Masaya Ogawa*

*Department of Applied Chemistry, Faculty of Engineering,
Kansai University, Senriyama, Suita, Osaka 564, Japan*

Received May 21, 1985

A more direct synthesis of bis(cyclopentadienyl)zirconium dihydride, Cp_2ZrH_2 (**1**), has been reported relatively recently by Wailes et al.[1] They have also reported in their subsequent papers[2-4] that **1** reacts with acetone to give bis(cyclopentadienyl)zirconium diisopropoxide, $Cp_2Zr[OCH(CH_3)_2]_2$ (**2**), and with 2-propanol to give **2** and zirconium tetraisopropoxide, $Zr[OCH(CH_3)_2]_4$, in which the

---

(1) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405.

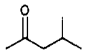
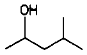
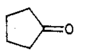
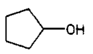
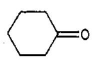
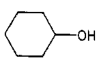
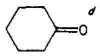
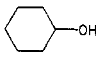
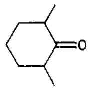
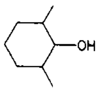
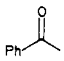
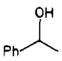
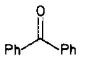
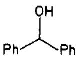
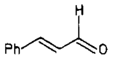
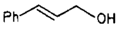
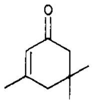
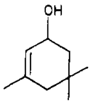
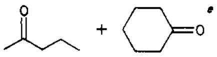
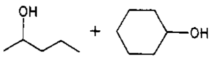
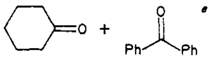
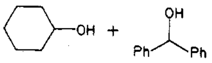
(2) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 413.

(3) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1972**, *43*, C29.

(4) Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1972**, *43*, C32.

0022-3263/86/1951-0240$01.50/0

Table I. Cp_2ZrH_2-Catalyzed Reductions of Ketones with 2-Propanol[a]

ketone		yield (%)[b]	
		alcohol	condensatn product[c]
		66	1.1
		82	5.0
		87	3.9
[d]		99	
		92	0.9
		78	trace
		96	0.6
		61	trace
		49	1.0
[e]		6 + 75	15.0
[e]		13 + 76	12.1

[a] Ketone, 2-propanol, and Cp_2ZrH_2 (1:2:0.02 molar ratio) were allowed to react at 130 °C for 6 h. [b] Determined by VPC. [c] Self- and cross-condensation products were included. [d] 2-Propanol (5 equiv) was used. [e] Equimolar mixture at 150 °C.

cyclopentadienyl groups are split off.[3]

However, when 1 was allowed to react in the presence of both a ketone and an alcohol, the hydrogen transfer from the alcohol to the ketone occured, i.e., Meerwein–Ponndorf–Verley (MPV) type reduction of ketone and Oppenauer (OPP) type oxidation of alcohol were simultaneously completed by 1 in the same reaction system.

Table I shows the reductions of some ketones with 2-propanol catalyzed by 1.

All of the ketones used were reduced to the corresponding alcohols in good yields. But the reduction of 4-methyl-2-pentanone afforded 4-methyl-2-pentanol in somewhat low yield (66%). The sterically hindered ketone, 2,6-dimethylcyclohexanone, was fairly reduced without any significant steric hindrance. α,β-Unsaturated compounds, such as cinnamaldehyde and isophorone, were slowly reduced to the corresponding unsaturated alcohols.

In the reactions using equimolar quantities of 2-propanol and ketone, a small amount of aldol type condensation products were formed. But the contamination with the condensation products was suppressed if excess 2-propanol (5 times the amounts of ketone) was used. Reductions of equimolar mixtures of two kinds of ketones showed that the ease with which this type of reduction occurs was in the decreasing order of aromatic, alicyclic, and aliphatic ketones.

In general, it is known that the MPV reduction[5] of carbonyl compounds calls for the addition of at least 100% to 200% excess aluminum alkoxide and that the resulting intermediate aluminum derivative of ketone must be hydrolyzed with acid to generate the alcohol. In the present reaction, however, a catalytic amount of 1 (0.02 equiv) was sufficient to reduce the carbonyl compounds and the products were obtained without hydrolysis with acid.

Table II. Cp_2ZrH_2-Catalyzed Oxidations of Alcohols with Carbonyl Compounds[a]

				yield (%)[c]	
alcohol	hydrogen acceptor[b]	aldehyde	or	ketone	condensatn product
butanol	Bz	butanal		45	1.5
2-butanol	Bz	2-butanone		66	1.1
octanol	Bz	octanal		68	trace
2-octanol	Bz	2-octanone		81	
dodecanol[d]	B	dodecanal		70	
octadecanol[d]	B	octadecanal		58	
cyclohexanol	A	cyclohexanone		61	17.0
benzyl alcohol	B	benzaldehyde		74	
allyl alcohol	B	acrolein		96	trace
geraniol	B	geranial		92	

[a] Alcohol, hydrogen acceptor, and Cp_2ZrH_2 (1:1:0.02 molar ratio) were allowed to react at 130 °C for 6 h. [b] Bz, benzaldehyde; A, acetone; B, benzophenone. [c] Isolated yield. [d] At 150 °C.

On the contrary, various alcohols were oxidized to the corresponding carbonyl compounds by 1 in the presence of an appropriate carbonyl compound which serves as hydrogen acceptor. Table II shows the oxidation results of some kinds of alcohols.

Similarly the oxidation of alcohols as mentioned in the reduction of ketones was prompted by using 0.02 equiv of 1, while OPP oxidation[6] required usually 1 to 3 equiv of aluminum alkoxide. Acetone, considered to be a suitable hydrogen acceptor, was inadequate owing to the formation of the condensation product of acetone itself, mesityl oxide. Thus, benzaldehyde or benzophenone which serves as satisfactory hydrogen acceptor was employed for the present oxidations.

All the oxidation of alcohols proceeded smoothly to give the expected carbonyl compounds. Especially, primary alcohols, which are oxidized with difficulty by the OPP method, could be easily oxidized to the corresponding aldehydes in substantial yields. This is noteworthy in connection with the preparation of long-chain aldehydes which have been made via a more troublesome process from acid chloride.[7] Further, α,β-unsaturated alcohols, such as allyl alcohol and geraniol, were converted to the corresponding unsaturated aldehydes in almost theoretical yields, giving acrolein and geranial having the same configuration as geraniol, respectively.

In order to test the synthetic usefulness of this method, the reductions of cyclohexanone with 2-propanol were repeatedly examined by the use of zirconium species[8] recovered from the reaction mixture by filtration after the reaction. The conversion of cyclohexanone to cyclohexanol by the recovered zirconium species decreased gradually with the number of runs increased, but cyclohexanol was obtained in about 70% yield even by eight repetitions of the runs.

In conclusion, the present MPV type reduction and OPP type oxidation catalyzed by 1 are very useful, since 1 can be easily prepared from the commercially available bis(cyclopentadienyl)zirconium dichloride, Cp_2ZrCl_2, and the

---

(5) Wilds, A. L. *Org. React. (N.Y.)* **1944**, *2*, 178.

(6) Djerassi, C. *Org. React. (N.Y.)* **1951**, *6*, 207.

(7) Bartlett, P. D.; Giddings, W. P. *J. Am. Chem. Soc.* **1960**, *82*, 1240.

(8) The detailed mechanism for hydrogen transfer from alcohol to carbonyl compound by 1 is still uncertain, but the reaction may proceed via an alkoxyzirconium species.

J. Org. Chem. 1986, 51, 242–245

recovered zirconium species can be repeatedly used as the catalyst without any treatment.

Experimental Section

The melting points were determined on a Yanaco MP-52032 apparatus and are corrected. The IR spectra were taken with a JASCO A-202 spectrometer and the ^{1}H and ^{13}C NMR spectra were recorded on a JEOL PMX-60 and a Hitachi R-90H spectrometer, respectively. The GLC analyses were performed on a Yanaco G-1800 instrument with a 3 m × 2.5 mm column packed with 5% Silicone OV-7 on Chromosorb W.

Materials. Bis(cyclopentadienyl)zirconium dihydride (1) was prepared by the Wailes procedure:[1] mp 304–305 °C (lit.[1] mp 305 °C); IR (KBr) 3100, 1520, 1300, 1020, 840 cm^{-1}.

The compounds were of commercial grade, and the solvents were used after dehydration by conventional methods.

Reduction of Carbonyl Compounds by 1. Carbonyl compound (10 mmol), 2-propanol (20 mmol), and 1 (0.2 mmol) were placed in an autoclave (50 cm^3) under an argon atmosphere, and the reaction was carried out with mechanical shaking at 130 °C for 6 h. After removal of catalyst by filtration, the product was isolated by distillation or by MPLC on silica gel (hexane/ethyl acetate = 5:1 eluent). The spectral data of the reaction products agreed with those of authentic samples and literature values.[9,10]

Oxidation of Alcohols by 1. Alcohol (10 mmol), carbonyl compound (10 mmol), and 1 (0.2 mmol) were placed in an autoclave under an argon atmosphere. The reactions were carried out in a similar manner as above, and the products were identified by comparison of their spectral data with those of authentic samples and literature values.[11]

Registry No. Bis(cyclopentadienyl)zirconium dihydride, 37342-98-6; 2-propanone, 67-64-1; 4-methyl-2-pentanone, 108-10-1; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; 2,6-dimethylcyclohexanone, 2816-57-1; acetophenone, 98-86-2; benzophenone, 119-61-9; 3-phenyl-2-propenal, 104-55-2; 3,5,5-trimethyl-2-cyclohexen-1-one, 78-59-1; 2-pentanone, 107-87-9; 2-propanol, 67-63-0; 4-methyl-2-pentanol, 108-11-2; cyclopentanol, 96-41-3; cyclohexanol, 108-93-0; 2,6-dimethylcyclohexanol, 5337-72-4; 1-phenylethanol, 98-85-1; diphenylmethanol, 91-01-0; 3-phenyl-2-propen-1-ol, 104-54-1; 3,5,5-trimethyl-2-cyclohexen-1-ol, 470-99-5; 2-pentanol, 6032-29-7; 1-butanol, 71-36-3; 2-butanol, 78-92-2; 1-octanol, 111-87-5; 2-octanol, 123-96-6; 1-dodecanol, 112-53-8; 1-octadecanol, 112-92-5; benzyl alcohol, 100-51-6; allyl alcohol, 107-18-6; geraniol, 106-24-1; butanal, 123-72-8; 2-butanone, 78-93-3; octanal, 124-13-0; 2-octanone, 111-13-7; dodecanal, 112-54-9; octadecanal, 638-66-4; benzaldehyde, 100-52-7; acrolein, 107-02-8; geranial, 141-27-5.

---

(9) Simons, W. W.; Zanger, M. "The Sadtler Guide to NMR Spectra"; Sadtler Research Laboratories: Philadelphia, 1972; p 232.

(10) Pouchert, C. J.; Campbell, J. R. "The Aldrich Library of NMR Spectra"; Aldrich Chemical Company: WI, 1974; Vol. 1, 149D.

(11) Green, G.; Gliffith, W. P.; Holinshead, D. M.; Ley, S. V.; Schröder, M. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 681.

Simple Access to Highly Enantiomerically Enriched (*S*)-3-Methyl-1-pentanol, (*S*)-3-Methyl-1-pentene, (2*R*,3*S*)-2-Deuterio-3-methyl-1-pentanol, and (2*S*,3*S*)-3-Methyl-2-pentanol from Natural L-Isoleucine

Volker Schurig,* Ulrich Leyrer, and Dorothee Wistuba

Institut für Organische Chemie, Universität Tübingen, D 74 Tübingen, West Germany

Received February 19, 1985

The smallest chiral, aliphatic hydrocarbon residue, i.e., the *sec*-butyl group, occurs in essentially quantitative enantiomeric purity[1] in L-isoleucine [(2*S*,3*S*)-2-amino-3-methylpentanoic acid 1]. As has been established by anomalous X-ray diffraction in the pioneering work of Trommel and Bijvoet[3] the absolute configuration of the *sec*-butyl group in unnatural D-isoleucine is *R*. We describe here the transformation of the "chiral carbon pool" compound L-isoleucine (1) into some small chiral molecules containing the (*S*)-*sec*-butyl group (cf. Scheme I). The configurational composition of the compounds prepared is unequivocal established by modern chromatographic and spectroscopic (^{2}H-NMR) methods.

According to Scheme I L-isoleucine (1) is transformed via diazotization (HCl, NaNO$_2$)[4,5] into (2*S*,3*S*)-2-chloro-3-methylpentanoic acid (2). We have recently shown that this reaction proceeds with a high degree of stereointegrity, i.e., with 99.5% (!) of net retention of configuration at C-2, and with virtually no racemization at C-3 of the *sec*-butyl group.[2,5] Exhaustive reduction of 2 via route 1 furnishes the chiral primary alcohol (*S*)-3-methyl-1-pentanol (3) in 82% chemical yield.[5] This alcohol has previously been obtained by Pino et al.[6] via chain extension from (*S*)-2-methyl-1-butanol, and racemization to an unknown extent was believed to have occurred in their procedure. According to Pino et al.[6] the olefin (*S*)-3-methyl-1-pentene (5) (which was prepared from 3 on pyrolysis of the acetate 4) was contaminated with 2.6% of 4-methyl-1-pentene arising from 3-methyl-1-butanol (occurring as contaminant of the starting alcohol 2-methyl-1-butanol).

In contrast, (*S*)-3-methyl-1-pentene (5) obtained from L-isoleucine 1 according to route 1 (Scheme I) is free of olefinic isomers. Its enantiomeric purity and that of the precursor, the alcohol 3, has been established by two independent chromatographic methods. Thus, ee = 98.6% for (*S*)-3-methyl-1-pentene (5) has been determined by HPLC of the diastereomeric platinum olefin π complex *trans*-chloro-(*N*,*N*-dimethyl-D-phenylglycin)(η_2-(3*S*)-3-methyl-1-pentene)platinum(II).[7,8] In addition, a sample of 5 has been epoxidized with *m*-chloroperbenzoic acid to the diastereomeric oxiranes 8 (55%) and 9 (45%), which can be quantitatively resolved by complexation gas chromatography[5] on optically active nickel(II) bis(2-heptafluorobutyryl)-(1*S*)-4-methyl-thujan-3-onate).[9] For both 8 and 9 an enantiomeric purity of 98.8 ± 0.2% has been determined. Since no crystallization steps have been involved in the conversion of 3 to 5 and of 5 to 8 and 9, respectively, it is obvious that the alcohol 3 and the olefin 5 were also *at least* 98.8% enantiomerically pure. By comparison of our specific rotation of (*S*)-3-methyl-1-pentene (5), i.e., $[\alpha]^{17}_{\mathrm{D}}$ +33.72°, α^{17}_{D} +2.28° (l = 0.1 dm, neat), d^{17}_{4} 0.6703[6] (neat), ee = 98.8%, with that given by Pino et al.,[6] i.e. $[\alpha]^{17}_{\mathrm{D}}$ +32.86°, it follows that their product had actually an enantiomeric purity of 96.4%, instead of an assumed purity of only 86%.[6]

Reduction of 2 via route 2 (Scheme I) furnishes the

---

(1) The configurational composition of a typical specimen of commercial L-isoleucine has been determined gas chromatographically on Chirasil-Val to 99.7% (2*S*,3*S*)-2-amino-3-methylpentanoic acid, 0.2% (2*S*,3*R*)-2-amino-3-methylpentanoic acid, 0.1% (2*R*,3*S*)-2-amino-3-methylpentanoic acid, and approximately 0% (2*R*,3*R*)-2-amino-3-methylpentanoic acid.[2]

(2) Koppenhoefer, B.; Schurig, V., submitted for publication in *Org. Synth.*

(3) Trommel, J.; Bijvoet, J. M. *Acta Crystallogr.* **1954**, *7*, 703–709.

(4) Fu, S.-C.; Birnbaum, S. M.; Greenstein, J. P. *J. Am. Chem. Soc.* **1954**, *76*, 6054–6058.

(5) Koppenhoefer, B.; Weber, R.; Schurig, V. *Synthesis* **1982**, 316–318.

(6) Pino, P.; Lardicci, L.; Centoni, L. *J. Org. Chem.* **1959**, *24*, 1399–1404.

(7) Goldman, M.; Kustanovich, Z.; Weinstein, S.; Tishbee, A.; Gil-Av, E. *J. Am. Chem. Soc.* **1982**, *104*, 1093–1095.

(8) Retzbach, H. *Diploma Thesis*, University of Tübingen, 1982.

(9) Hintzer, K. *Thesis*, University of Tübingen, 1983.

0022-3263/86/1951-0242$01.50/0