

DIPHENYLBORANE. A NEW HYDROBORATING AGENT. SYNTHESIS OF ALKYLDIPHENYLBORANES AND THEIR APPLICATION TO THE CONJUGATE ADDITION REACTION OF ORGANOBORANES *

PEYTON JACOB, III **

Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907 (U.S.A.)

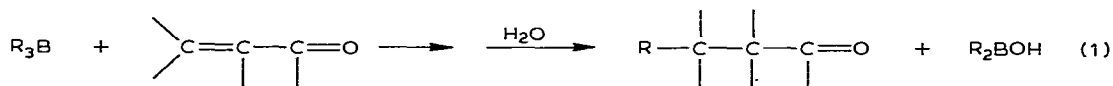
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Summary

Diphenylborane, prepared in situ by the reaction of methyl diphenylborinate with lithium aluminum hydride, reacts readily with olefins to provide the corresponding alkyldiphenylboranes. Diphenylborane generated by the reaction of boron trifluoride etherate with pyridinediphenylborane likewise reacts with olefins to give alkyldiphenylboranes. The latter method is suitable for the hydroboration of olefins containing functional groups. Alkyldiphenylboranes react with methyl vinyl ketone affording good to excellent yields of the corresponding 4-alkyl-2-butanones. The advantages for the use of alkyldiphenylboranes in the conjugate addition reactions of organoboranes are discussed.

Introduction

The conjugate addition of trialkylboranes to α,β -unsaturated carbonyl compounds is one of the more general and synthetically useful reactions that organoboranes will undergo (eq. 1) [1,2].

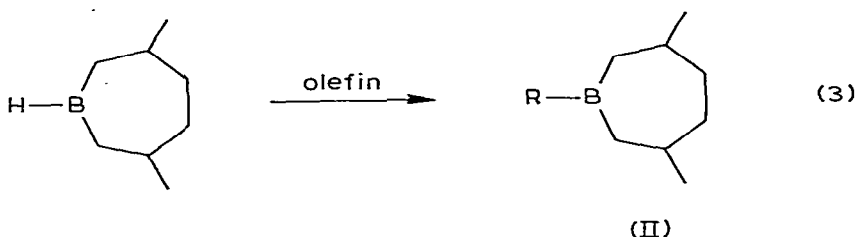
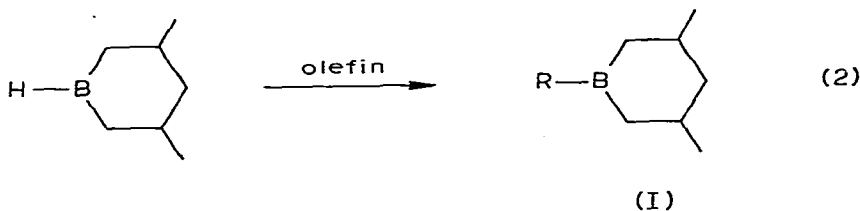


This reaction has been used to transfer primary, secondary, and tertiary alkyl groups to a wide variety of unsaturated aldehydes and ketones. However, only one of the three alkyl groups can be transferred from the organoborane. This can be a serious limitation in synthetic applications, since the maximum yield based on available alkyl groups is 33%.

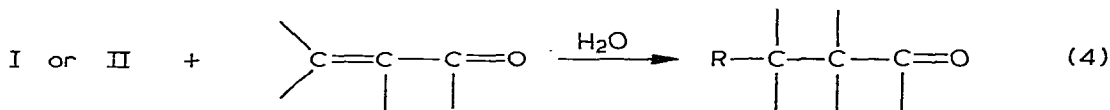
* Dedicated to Prof. H.C. Brown on the occasion of his 66th birthday.

** Present address: Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94143 (U.S.A.).

Recently, a partial solution to this problem was developed in our laboratories. [3]. Certain readily synthesized boracyclanes react with olefins to provide the corresponding *B*-alkyl derivative in high yield (eq. 2 and 3). These derivatives



(I and II) undergo conjugate addition to α,β -unsaturated carbonyl compounds with selective transfer of the *B*-alkyl group, provided that the alkyl group is secondary or tertiary (eq. 4). If the alkyl group is primary, the yield of alkylated



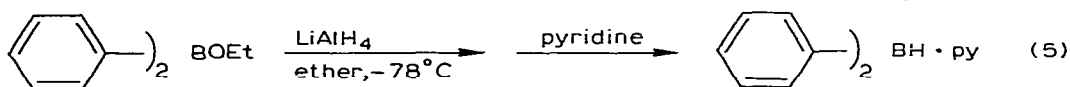
R = secondary or tertiary alkyl

product is considerably lower due to competitive reaction of the boracyclane moiety*.

In the course of our studies on the conjugate additions and related free-radical reactions of organoboranes, we found that triphenylborane would not react with methyl vinyl ketone [4]. Furthermore, when methyl vinyl ketone was added to a mixture of tri-*n*-butylborane and triphenylborane, the tri-*n*-butylborane underwent complete reaction leaving the triphenylborane unreacted. This result suggested that a "mixed" organoborane containing both alkyl and aryl groups would transfer the alkyl group selectively in the conjugate addition reaction, even if the alkyl group were primary. Therefore, we decided to explore the possibility of hydroborating olefins with diphenylborane as a route to alkyl diphenylboranes.

The preparation of diphenylborane and isolation as the pyridine complex has been reported by Hawthorne [5] (eq. 5).

* The conjugate addition reaction involves the displacement of an alkyl radical from the organoborane. It appears that the alkyl group which gives rise to the more stable free-radical is displaced preferentially from mixed organoboranes [2].



In a similar fashion, Hawthorne has prepared amine adducts of several ring-substituted diphenylboranes [6]. However, to our knowledge the hydroboration of olefins with diphenylborane or any of its derivatives has not been reported.

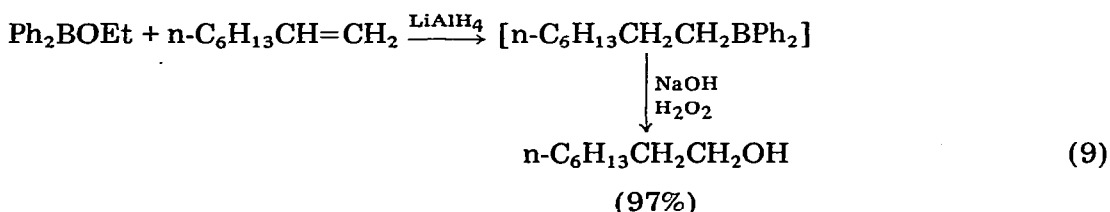
Recently, several general methods for the synthesis of mixed trialkylboranes have been developed in our laboratories [7,8]. These methods depend upon the in situ generation of a dialkylborane, which is trapped by an olefin to give the mixed trialkylborane (eq. 6-8).



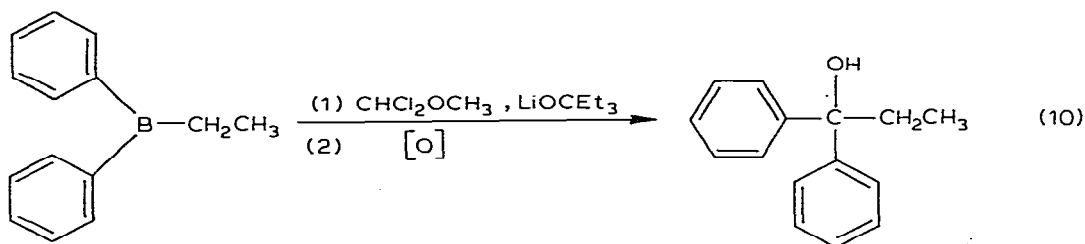
Since esters of diphenylborinic acid [5,9] (Ph_2BOR) and pyridinediphenylborane [5] ($\text{Ph}_2\text{BH} \cdot \text{py}$) are readily available compounds, application of the above methods to the synthesis of alkyl diphenylboranes appeared feasible.

Results and discussion

Hydroboration of olefins with diphenylborane generated by the reaction of lithium aluminum hydride (LiAlH_4) with ethyl diphenylborinate. The addition of lithium aluminum hydride to a solution of ethyl diphenylborinate and 1-octene in THF resulted in a rapid disappearance of the olefin. The usual oxidation with alkaline hydrogen peroxide provided 1-octanol in 97% yield (eq. 9). Thus it is apparent that diphenylborane generated via hydride transfer from lithium aluminum hydride to the borinate ester is an active hydroborating agent.



The reduction of ethyl diphenylborinate was then carried out in the presence of ethylene. Ethyldiphenylborane was isolated from the reaction mixture by distillation and characterized by its PMR spectrum and by conversion into ethyldiphenylcarbinol via the DCME* reaction [10] (eq. 10). The isolation and charac-



* DCME = dichloromethyl methyl ether.

TABLE 1

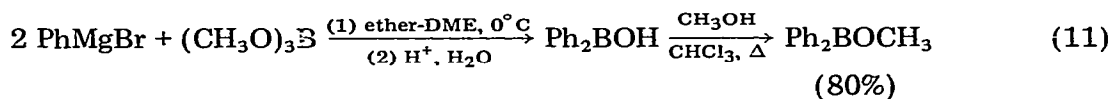
STOICHIOMETRY OF THE REACTION OF LITHIUM ALUMINUM HYDRIDE WITH METHYL DIPHENYLBORINATE IN THE PRESENCE OF 1-OCTENE ^a

Ph ₂ BOCH ₃ (mmol)	1-Octene (mmol)	LiAlH ₄ (mmol)	"Hydride" (mmol)	1-Octanol yield (%) ^b
6.00	5.00	2.50	10.0	94
6.00	5.00	1.67	6.68	95
6.00	5.00	1.25	5.00	70

^a The hydroboration was carried out for 1 h at 25°C. ^b Yield by GLPC analysis after oxidation.

terization of ethyldiphenylborane was gratifying in light of a report that certain mixed boranes containing both phenyl and alkyl groups undergo rapid symmetrization to triphenylborane and trialkylborane [11].

The hydroboration of olefins with diphenylborane generated by the reaction of lithium aluminum hydride with methyl diphenylborinate. The Ph₂BOR/LiAlH₄ route to diphenylborane seemed promising and was investigated further. We found that the methyl ester of diphenylborinic acid can be prepared easily on a large scale by a modification of Hawthorne's synthesis of ethyl diphenylborinate [5]. The crude borinic acid obtained through the Grignard reaction can be esterified directly via an azeotropic distillation with methanol and chloroform to provide the methoxy derivative in high yield (eq. 11).



The addition of LiAlH₄ to a mixture of 1-octene and methyl diphenylborinate resulted in a rapid reaction, and an essentially quantitative yield of 1-octanol was obtained after oxidation. In a similar fashion, a few other representative olefins (e.g. cyclopentene, 2-methyl-1-butene) were converted into the corresponding alcohols in high yield. Under these mild conditions (25°C, 1 h) it was found that three of the four "hydrides" of lithium aluminum hydride may be utilized*. Consequently, application of this method necessitates the use of a slight excess of active hydride (Table 1).

Hydroboration of olefins with diphenylborane generated by the reaction of pyridinediphenylborane with boron trifluoride etherate. Hydroboration is a mild reaction, and a variety of functional groups (e.g. ester, nitrile, halogen) on the olefin can be tolerated [1]. However, the Ph₂BOR/LiAlH₄ method of hydroboration would not be expected to tolerate reducible functional groups. We therefore sought a means for carrying out the hydroboration of functionally-substituted olefins with diphenylborane. It appeared that the use of the pyridine complex of diphenylborane might solve this difficulty. Although there was very little reaction between pyridinediphenylborane and 1-octene after 1 h in THF, the addition of 1 equivalent of boron trifluoride etherate resulted in a rapid disappearance of the olefin. Furthermore, it was found that the reaction could

* The analogous reaction of methyl dialkylborinates with LiAlH₄ likewise utilizes three of the four "hydrides" [7].

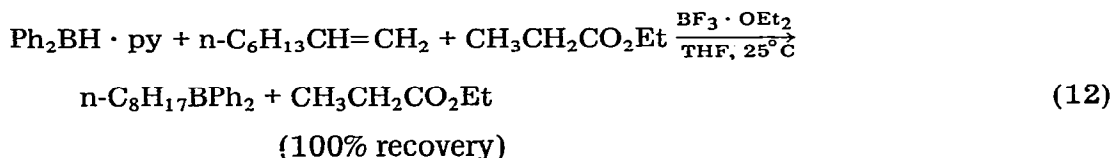
TABLE 2

CONVERSION OF OLEFINS INTO 4-ALKYL-2-BUTANONES BY THE REACTION OF THE CORRESPONDING ALKYLDIPHENYLBORANES WITH METHYL VINYL KETONE ^a

Olefin	Product	Yield (%) ^b	
		Procedure A	Procedure B
1-Octene	2-Dodecanone	95	73
Cyclopentene	4-Cyclopentyl-2-butanone	100	
2-Methyl-1-butene	6-Methyl-2-octanone	97	
4-Vinylcyclohexene	6-(3-Cyclohexenyl)-2-hexanone	(76) ^c	
5-Acetoxy-1-pentene	9-Acetoxy-2-nonanone		63

^a In procedure A the Ph₂BOCH₃/LiAlH₄ method of hydroboration was used. In procedure B the Ph₂BH · py/BF₃ · OEt₂ method of hydroboration was used. ^b Yield by GLPC analysis. ^c Isolation yield.

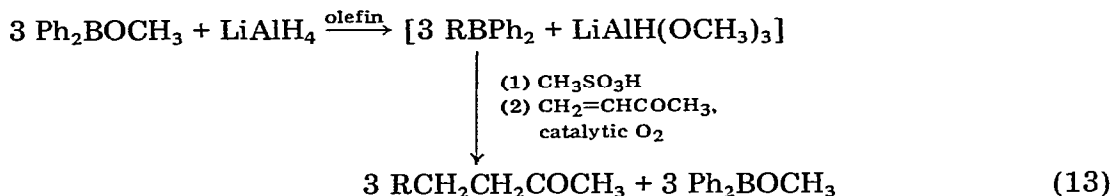
be carried out in the presence of ethyl propionate with complete recovery of the ester (eq. 12).



Consequently this method should be applicable to the hydroboration of olefins containing the ester functionality. In all probability, less reactive functional groups such as nitrile and halogen will also be tolerated by the reaction.

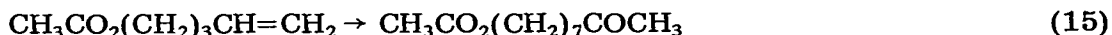
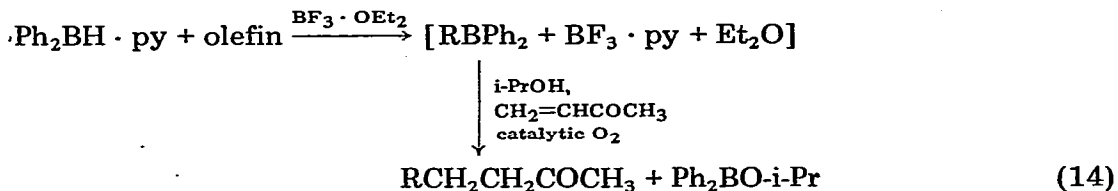
Reaction of alkyldiphenylboranes with methyl vinyl ketone. We were now in a position to apply the alkyldiphenylboranes to the conjugate addition reaction. Several representative olefins were hydroborated by the methods described above, and the resulting boranes reacted with methyl vinyl ketone. In every case the desired 4-alkyl-2-butanone was obtained, generally in excellent yield (Table 2). In no case was there evidence for the formation of 4-phenyl-2-butanone, the product of phenyl transfer. Consequently, transfer of the alkyl group in these reactions must be highly selective.

Two general procedures were utilized. In Procedure A, the Ph₂BOR/LiAlH₄ hydroboration method was used. Following the hydroboration, methanesulfonic acid was added to destroy excess hydride and aluminum alkoxides. Then methyl vinyl ketone was added and the 1,4-addition reaction was carried out using air catalysis * (eq. 13).

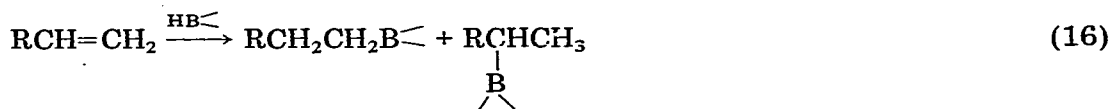


* Although the conjugate addition did proceed under oxygen-free conditions, the rate of reaction was greatly increased by the introduction of air. Other free-radical reactions of organoboranes are also catalyzed by oxygen [2].

Procedure B utilized the $\text{Ph}_2\text{BH} \cdot \text{py} / \text{BF}_3 \cdot \text{OEt}_2$ method of hydroboration. After the hydroboration stage, the conjugate addition was accomplished by adding methyl vinyl ketone and isopropyl alcohol to protonolyze the intermediate enol borinate (eq. 14). This procedure was successfully applied to an olefinic ester (eq. 15).

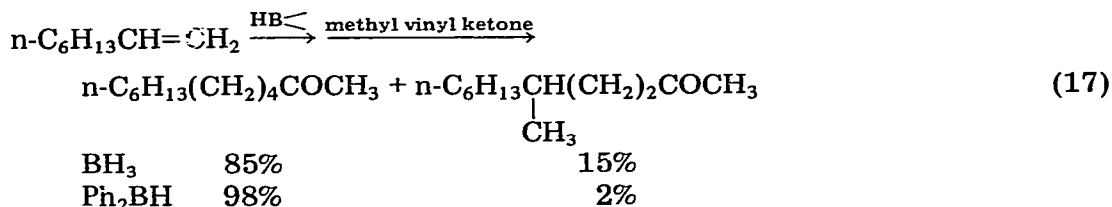


Besides the obvious advantage that a high yield based on olefin can be obtained, there is another advantage for the use of diphenylborane in the conjugate addition reaction that is perhaps less obvious. Hydroborations with monofunctional hydroborating agents are generally much more regioselective than hydroborations with borane [1]. Thus, hydroboration of a terminal olefin such as 1-octene with borane places 94% of the boron in the 1-position and 6% of the boron in the 2-position. With diphenylborane only ~2% of the sec-alkyl derivative is formed (eq. 16). Since the sec-alkyl groups are transferred preferentially in the

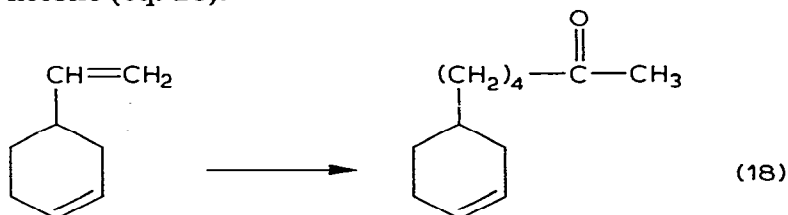


BH_3	94%	6%
Ph_2BH	98%	2%

conjugate addition reaction, the product derived from R_3B contains ~15% of the branched isomer [12]. However, using RBPh_2 only 2% of the branched isomer is obtained (eq. 17).



It is also possible to utilize the selectivity of hydroborations with diphenylborane to achieve the conversion of a diene into the corresponding unsaturated ketone (eq. 18).



In conclusion, diphenylborane has been shown to be an active hydroborating agent. The alkyldiphenylboranes, prepared by hydroboration of olefins with diphenylborane, react with methyl vinyl ketone with exclusive transfer of the alkyl groups. Consequently, high yields of the desired products based on starting olefins can be obtained. Furthermore, the high regioselectivity of hydroborations with diphenylborane in many cases leads to products of much higher isomeric purity than those obtained from the simple trialkylboranes. The successful application of the alkyldiphenylboranes to the conjugate addition reaction suggests that these reagents will be valuable in other free-radical reactions of organoboranes [2] as well.

Experimental

All glassware was oven-dried at 140°C for at least 2 h before use, assembled hot, and cooled under a flow of nitrogen. The organoboranes were always handled under nitrogen with careful protection from air and moisture *. Reagents and solvents were transferred via syringe or double-ended needle. PMR, IR, and mass spectra were obtained with a Varián T-60, a Perkin-Elmer 137B, and CEC 21-100, respectively. GLPC analyses were carried out using a Hewlett-Packard 5750 chromatograph. Microanalyses were performed by the Purdue Microanalytical Laboratory.

Materials. Ethyl diphenylborinate was prepared by Hawthorne's method [5]. A standard solution of lithium aluminum hydride in THF was prepared as described previously [14]. Methyl vinyl ketone and dichloromethyl methyl ether were obtained from the Aldrich Chemical Company and redistilled before use. Lithium triethylcarboxide [10] was prepared by adding triethylcarbinol to a standard solution of n-butyllithium in hexane. Boron trifluoride etherate was distilled from calcium hydride under reduced pressure. Methyl borate (Callery Chemical Company) was distilled from excess sodium. Phenylmagnesium bromide was prepared in ether in the usual manner and standardized by the method of Watson and Eastham [15]. Commercially available ethylene, 1-octene, cyclopentene, 2-methyl-1-butene, 4-vinylcyclohexene, 4-penten-1-ol acetate, and n-alkanes (internal standards) were used without further purification. Solvents were purified by standard methods.

Methyl diphenylborinate. A 2 l three-neck flask was fitted with a 500 ml dropping funnel and mechanical stirrer. The flask was flushed with nitrogen, charged with 500 ml dry 1,2-dimethoxyethane ** (DME) and 51.7 g (0.50 mol) methyl borate, then cooled to ca. -7°C with an ice-salt bath. Phenylmagnesium bromide (500 ml of 2.15 M, 1.07 mol) in ether was added with vigorous stirring over 90 min while maintaining the temperature between -7 and 0°C. A heavy precipitate formed during the course of the addition. After stirring 5 h at room temperature the reaction mixture was worked up by the careful addition of 6 M HCl (1.4 mol) with ice cooling. (At this point maintaining a nitrogen atmosphere was no longer necessary.) The organic layer was separated and the aqueous layer

* A description of techniques useful in handling organoboranes and other air-sensitive compounds is given in ref. 13.

** Attempts to carry out the reaction using ether or THF as the solvent were unsuccessful.

was extracted with 100 ml ether. The solvent was removed (rotary evaporator) from the combined organic phases, and the crude borinic acid was esterified by azeotropic distillation with chloroform (960 ml) and methanol (240 ml). A vacuum distillation (under nitrogen) provided 6.9 g (forerun) b.p. 87–88°C (0.1 mmHg), 71.2 g (main fraction) b.p. 88–91°C (0.1 mmHg), total yield 78.1 g (80%) of methyl diphenylborinate (lit. [10] b.p. 132°C at 10 mmHg), PMR (CCl₄, TMS) δ 3.8 (s, 3 H), 7.2–7.7 ppm (m, 10 H). The product contained approximately 5% biphenyl, but was satisfactory for most purposes. Methyl diphenylborinate free from biphenyl was obtained by purification of the borinic acid as the ethanalamine derivative according to Hawthorne's procedure [5]. Methyl diphenylborinate is moisture sensitive, but appears to be stable indefinitely when stored under an inert atmosphere.

Pyridinediphenylborane. The method is based on the previously reported synthesis of pyridinedialkylboranes [8] *. A solution of aluminum hydride [16] was prepared by adding 100% sulfuric acid (0.408 g, 4.17 mmol) dropwise with stirring to lithium aluminum hydride (8.33 mmol) in 15 ml THF at 0°C. After stirring 15 min at 0°C the solution of aluminum hydride was added via syringe to a stirred solution of methyl diphenylborinate (4.9 g, 25 mmol) and pyridine (2.1 g, 27 mmol) in anhydrous ether (40 ml) over 5 min at 0°C. The solution was stirred 1 h at room temperature, diluted with 20 ml pentane, and filtered through Celite under nitrogen pressure. The filter cake was washed with 40 ml benzene, and the combined filtrate and washings was concentrated under reduced pressure. The product was recrystallized from benzene/hexane (1/2, 50 ml), washed with pentane, and dried in vacuo. There was obtained 4.0 g (65%) of large colorless crystals, m.p. 107–108°C (lit. [5] m.p. 106–107°C). Crystalline pyridinediphenylborane is reported to be air stable [5], and was routinely transferred and weighed without protection from the atmosphere. As a precautionary measure, the borane was stored under nitrogen in tightly sealed glass bottles.

Ethyldiphenylborane. Ethyl diphenylborinate (5.0 g, 24 mmol) and 40 ml dry THF were placed in a 100 ml flask. The solution was cooled to 0°C and saturated with ethylene, introduced via a syringe needle placed below the surface of the rapidly stirred solution. A slow stream of ethylene was passed through the solution while 4.0 ml of 3.0 M lithium aluminum hydride (12 mmol) in THF was added over a 5 min period. The slow introduction of ethylene was continued for 1 h, then excess hydride was quenched with acetone (2 ml). Analysis by GLPC indicated the complete absence of triethylborane (symmetrization product). The solution was diluted with 40 ml pentane and centrifuged to remove aluminum salts. The supernate was distilled under nitrogen to provide 2.61 g (56% yield) of ethyldiphenylborane as a slightly yellow liquid, b.p. 85–87°C (0.080 mmHg), PMR (CCl₄, TMS) δ 1.1 (t, 3 H), 1.8 (q, 2 H), 7.3–7.8 ppm (m, 10 H).

Conversion of ethyldiphenylborane into 1,1-diphenylcarbinol via the DCME reaction. To a solution of ethyldiphenylborane (0.49 g, 2.5 mmol) and dichloromethyl methyl ether (0.35 g, 3 mmol) in 3 ml THF was added 6.0 ml of 1 M lithium triethylcarboxide (6 mmol) in hexane, dropwise with stirring at

* An attempt to prepare pyridinediphenylborane by Hawthorne's method (ref. 6) was unsuccessful.

0° C. After stirring 30 min at 25° C the reaction mixture was oxidized by the simultaneous addition of 3 M sodium acetate (3 ml) and 30% hydrogen peroxide (3 ml). The reaction mixture was stirred for 4 h at room temperature. After saturating the aqueous layer with anhydrous potassium carbonate analysis of the organic layer by GLPC revealed a 75% yield of 1,1-diphenyl-1-propanol. The product was identified by GLPC comparison with an authentic sample.

Reaction of alkylidiphenylboranes with methyl vinyl ketone by procedure A. The following procedure is representative. A 100 ml flask was charged with 20 ml THF, 2.16 g (20 mmol) of 4-vinylcyclohexene, and 4.5 g (23 mmol) of methyl diphenylborinate. The flask was cooled in an ice bath, and 5.72 ml of 1.28 M lithium aluminum hydride (7.33 mmol) was added dropwise with stirring over 10 min. The solution was stirred for 30 min at room temperature, then cooled to 0° C. Methanesulfonic acid (2.8 g, 29.3 mmol) was added dropwise (vigorous gas evolution) over 5 min. After stirring 10 min at 0° C, 1.56 g (22 mmol) of methyl vinyl ketone was added, and air was admitted at 0.5 ml/min via a syringe needle placed just above the rapidly stirred solution. After 1 h 20 ml of saturated aqueous sodium chloride was added. The aqueous layer was separated and extracted with 20 ml hexane. The combined organic layer was dried over anhydrous magnesium sulfate and distilled through a micro Vigreux column. There was obtained 2.73 g (76%) of 6-(3-cyclohexenyl)-2-hexanone, b.p. 74–76° C (0.1 mmHg), n_D^{20} 1.4719; semicarbazone m.p. 148–149° C; PMR (CCl₄, TMS) δ 1.2–2.2 (13 H), 2.0 (s, 3 H), 2.3 (t, 2 H), 5.6 ppm (m, 2 H); IR (neat) 1720 cm⁻¹. Mol. wt. Found: 180.151 (mass spectrum). C₁₂H₂₀O calcd.: 180.151.

The other reactions were carried out on a 5 mmol scale, and the products identified by GLPC comparison with authentic samples.

Reaction of alkylidiphenylboranes with methyl vinyl ketone procedure B. The following procedure is representative. To a 50 ml flask was added 1.35 g (5.5 mmol) of pyridinediphenylborane, 0.64 g (5 mmol) of 4-penten-1-ol acetate, and 5 ml THF. The solution was stirred at 0° C while 0.78 g (5.5 mmol) of boron trifluoride etherate was added over 5 min. After stirring 30 min at room temperature 0.39 g (5.5 mmol) of methyl vinyl ketone and 1 ml of isopropyl alcohol were added. Air was admitted at 0.5 ml/min via a syringe needle placed just above the rapidly stirred solution. After 1 h analysis by GLPC revealed a 63% yield of 9-acetoxy-2-nonanone. The product was isolated by preparative GLPC, n_D^{20} 1.4390; PMR (CCl₄, TMS) δ 1.2–1.7 (10 H), 1.9 (s, 3 H), 2.0 (s, 3 H), 2.3 (t, 2 H), 3.9 ppm (t, 2 H).

A small portion was converted to the semicarbazone, m.p. 93–94° C. Anal. Found: C, 56.04; H, 9.03. C₁₂H₂₃N₃O₃ calcd.: C, 56.01; H, 9.01%.

Acknowledgements

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