Efficient Synthesis of *B*-Iododialkyl- and *B*-Alkyldiiodoboranes as Their Acetonitrile Complexes: Application for the Enolboration–Aldolization of Ethyl Ketones

by **P. Veeraraghavan Ramachandran***, **Mu-Fa Zou**, and **Herbert C. Brown***

Herbert C. Brown Center for Borane Research, Department of Chemistry, Purdue University, West Lafayette, Indiana 47907-1393, USA
(phone: 765-494-5303; fax: 765-494-0239; e-mail: chandran@purdue.edu)

Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

A series of *B*-(iododialkyl)boranes and *B*-(alkyldiiodo)boranes have been readily synthesized as their MeCN complexes from the corresponding chloro- and bromoboranes by treatment with NaI or KI in MeCN. In the presence of $EtN(i\text{-}Pr)_2$, the *B*-(cyclohexyldiiodo)borane-acetonitrile complex converts ethyl ketones exclusively to the (*Z*)-enolates, which, upon aldolization with a series of aldehydes, provide the corresponding *syn*-aldols exclusively in high yields.

1. Introduction. – Of the several modified boranes available to the organic chemists, the haloboranes have found significant applications in organic syntheses [1]. For example, monochloroborane has been used for the preparation of dialkylchloroboranes, such as *B*-chloro(dicyclohexyl)borane and *B*-chloro(diisopinocampheyl)borane (*Aldrich: DIP-Chloride*™). The former reagent is efficient for the *anti*-selective enolboration–aldolization reaction [2], and the latter is an excellent reagent for the reduction of several classes of ketones in very high enantiomeric excess [3]. *B*-Chloro(dialkyl)boranes also act as intermediates in the synthesis of the corresponding alkylamines [4]. Dichloroborane has been used for the synthesis of the corresponding *B*-alkyldichloroboranes, which give rise to *syn*-selective enolboration–aldolization reactions [5]. Dichloroborane-methyl sulfide has been utilized for the reduction of alkyl or aryl azides to the corresponding amines [6]. Dibromoboranes have been used in the synthesis of (*E*)- or (*Z*)-alkenes or (*E*,*E*)-, (*E*,*Z*)-, or (*Z*,*Z*)-dienes at well [7]. Recently, we have reported the cleavage of epoxides with the bromoborane-methyl sulfide complex [8].

Although mono- and dichloro-, and mono- and dibromoboranes are commercially available as their methyl-sulfide complexes, the corresponding iodoboranes are not available. The synthesis of these iodoboranes involves the treatment of borane-methyl sulfide with I_2 in CS_2 [9]. The hydroboration of alkenes with iodoboranes is not always clean, though [10]. As an alternative, we treated dialkylboranes with I_2 [10], or applied the *Matteson* procedure [11], *i.e.*, the *in situ* hydroboration with triiodoborane and trimethylsilane, for the preparation of *B*-dialkyliodoboranes [12]. However, these procedures also failed to provide the corresponding *B*-alkyldiiodoboranes efficiently.

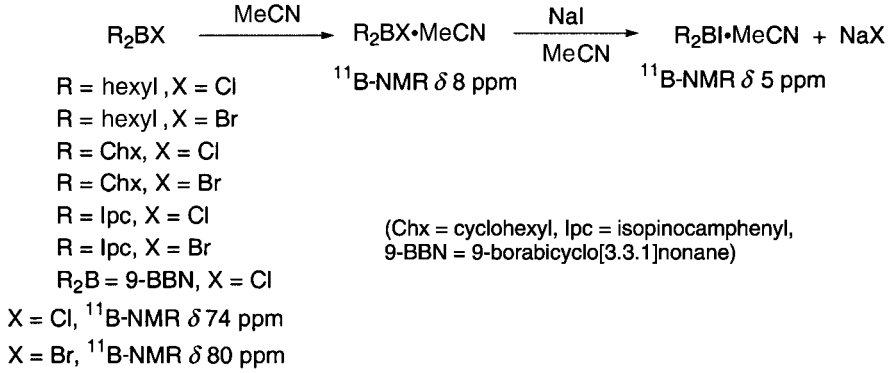
In contrast to *B*-alkylchloro- and *B*-alkylbromoboranes, the corresponding iodoboranes have been sparingly used in organic synthesis. This could be attributed

to the difficulties in their preparation and their lack of stability. We had shown that *B*-iododiisopinocampheylborane is an excellent reagent for the asymmetric ring-opening of *meso*-epoxides [13] and that *B*-dicyclohexyliodoborane is a *syn*-selective enolboration-aldolization reagent [14].

We have now found that both *B*-dialkyliodo- and *B*-alkyldiiodoboranes can be readily synthesized *via* a quantitative halogen-exchange reaction. Our successful synthesis of these iodoboranes and their application to the enolboration–aldolization reactions of ethyl ketones are reported herein.

2. Results and Discussion. – *Preparation of* B-*Dialkyliodoborane-Acetonitrile Complex*. Upon dissolving *B*-chlorodicyclohexylborane in MeCN, the ^{11}B-NMR spectrum revealed a shift from δ 74 to 8 ppm, indicating strong complex formation. Addition of 1.2 equiv. of NaI or KI dissolved in MeCN afforded a solid, presumably NaCl or KCl, respectively, and the ^{11}B-NMR spectra revealed a *singlet* at δ 5 ppm (*Scheme 1*). Although a downfield shift was expected in the NMR spectrum for the iodoborane compared to the chloroborane complex, the observed upfield shift may be attributed to a stronger MeCN complex with a superior *Lewis* acid.

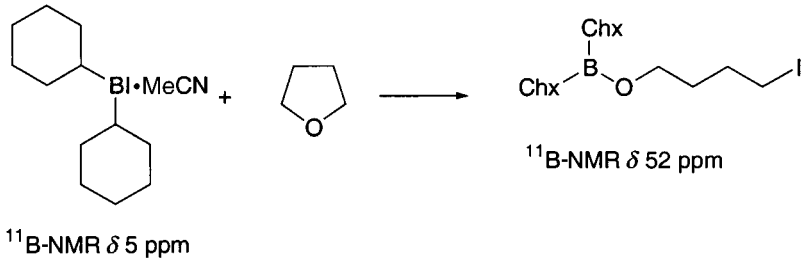
Scheme 1



Filtration of the inorganic salt and removal of MeCN provided a solid compound well-soluble in pentane, CH_2Cl_2, and CCl_4. However, upon dissolving in Et_2O or THF, the solution became warm, and the ^{11}B-NMR spectrum showed a peak at δ 52 ppm, indicating that, as expected, the iodoborane reagent had cleaved the ether (*Scheme 2*). Thus, we have discovered a *trans*-halogenation procedure for the synthesis of alkyliodoboranes. We applied this procedure to the synthesis of a series of *B*-alkyliodoboranes as their MeCN complexes from the corresponding chloro- and bromoboranes (*Scheme 1*).

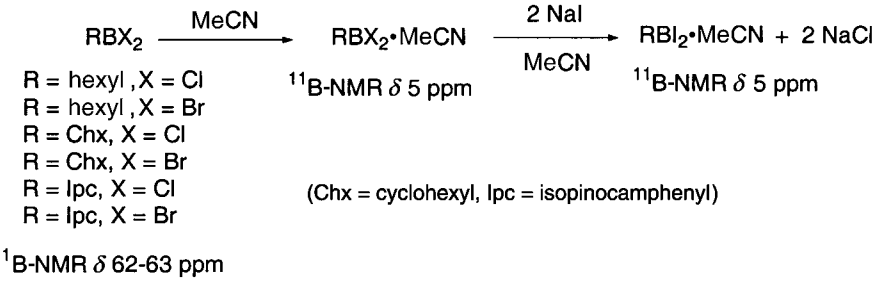
Preparation of B-*Alkyldiiodoboranes.* Although it should be possible to prepare *B*-alkyldiiodoboranes *via i*) the hydroboration of an alkene with diiodoborane-methyl sulfide [9], *ii*) the addition of I_2 to the corresponding alkylborane (RBH_2), or *iii*) *Matteson*'s trimethylsilane reduction of the corresponding dichloroborane, we experienced difficulties in obtaining pure *B*-alkyldiiodoboranes with all of the above procedures. We, therefore, applied the new *trans*-halogenation procedure for the

Scheme 2



synthesis of *B*-alkyldiiodoboranes. The ^{11}B-NMR spectrum of *B*-dichlorocyclohexylborane in MeCN revealed a signal at δ 6 ppm as compared to 62 ppm in pentane or CH_2Cl_2. Treatment of this complex with 2.5 equiv. of NaI or KI in MeCN also led to the precipitation of a solid, presumably NaCl or KCl, respectively. Surprisingly, unlike in the case of the *B*-dialkyliodoborane-acetonitrile complex, the ^{11}B-NMR spectrum exhibited no change (*Scheme 3*). However, THF was instantaneously cleaved (^{11}B-NMR: δ 31 ppm), revealing that the conversion to the diiodoborane-acetonitrile complex had occurred.

Scheme 3



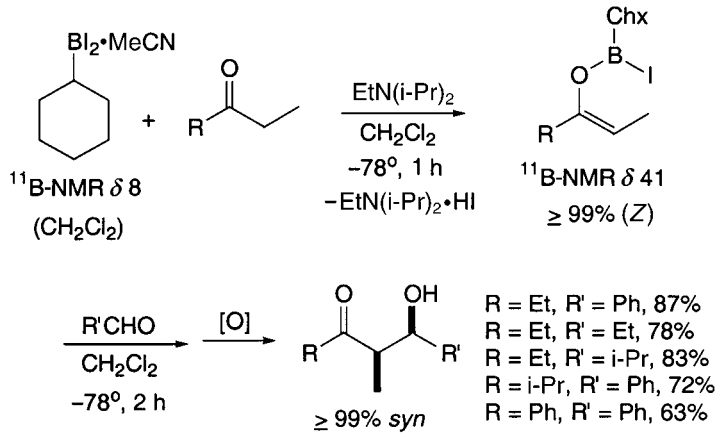
Removal of the solvent (MeCN) provided a solid mixture of $ChxBI_2 \cdot MeCN$, NaCl, and NaI. Chemically pure $ChxBI_2 \cdot MeCN$ was obtained by selective dissolution in CH_2Cl_2, followed by filtration and removal of the solvent. The solubility of $ChxBI_2 \cdot MeCN$ was examined next. Unlike $Chx_2BI \cdot MeCN$, $ChxBI_2 \cdot MeCN$ does not dissolve in hexanes. However, it readily dissolves in MeCN and CH_2Cl_2. The ^{11}B-NMR spectra of $ChxBI_2 \cdot MeCN$ in these solvents revealed peaks at δ 6 and 8 ppm, respectively. A series of *B*-alkyldiiodoboranes were prepared from the corresponding *B*-alkyldichloro- and *B*-alkyldibromoboranes (*Scheme 3*).

With the above mono- and dialkyliodoborane-acetonitrile complexes in our hands, we decided to examine their utility in organic synthesis. We reported earlier that *B*-dicyclohexyliodoborane is an efficient (*Z*)-enol- and *syn*-aldol-producing reagent [14]. Although we have already reported the utility of *B*-alkyldichloro- and *B*-alkyldibromoboranes [5], we could not test the corresponding diiodoboranes since none of our earlier procedures afforded the pure reagent.

Hence, we decided to examine $ChxBI_2 \cdot MeCN$ for the enolboration–aldolization reaction.

Enolboration–Aldolization with $ChxBI_2 \cdot MeCN$ Complex. Addition of $EtN(i\text{-}Pr)_2$ (1 equiv.) to the brown solution of $ChxBI_2 \cdot MeCN$ in CH_2Cl_2, followed by ^{11}B-NMR-spectroscopic analysis, revealed a *singlet* at δ 12 ppm, indicating that the amine probably displaces MeCN from the complex. We used the amine complex for the enolboration of diethyl ketone in CH_2Cl_2 at $-78°$. The mixture was stirred for 1 h, followed by addition of PhCHO at $-78°$. After 2 h, the mixture was quenched with phosphate buffer (pH 7.0) and oxidized (H_2O_2). ^{1}H-NMR Analysis of the crude product revealed the exclusive formation of the *syn*-aldol, thus providing the evidence that the enolization was $\geq$99% stereoselective (*Scheme 4*). Distillation provided an 87% yield of the pure product.

Scheme 4



The general character of the *syn*-selective aldol reaction with *B*-cyclohexyldiiodoborane reagent was further examined with a branched-chain ketone, *i.e.*, 2-methylpentan-3-one, and an aralkyl ketone, *i.e.*, propiophenone, which were reacted with PhCHO, propionaldehyde, and isobutyraldehyde. Exclusive formation of *syn*-aldols was observed in all these cases. In the case of 2-methylpentan-3-one, the enol borinate was formed solely on the ethyl side ($\geq$99% regioselectivity).

When the enolization of 1-phenylbutan-2-one was carried out under the standard conditions, no regioselectivity was observed. Enolboration occurred at both sides of the C=O group (*Scheme 5*). Nevertheless, the resulting α-substituted β-hydroxyketones were found to be exclusively *syn*-configured.

In summary, we have described a facile method for the preparation of *B*-dialkyliodoboranes and *B*-alkyldiiodoboranes as their MeCN complexes *via* a halogen-exchange reaction. *B*-Cyclohexyldiiodoborane is a versatile reagent for the *syn*-selective enolboration of a series of ethyl ketones.

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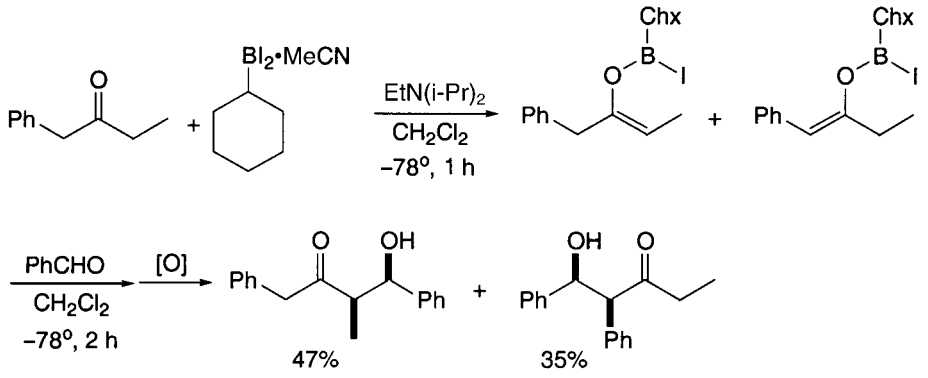
Scheme 5



Experimental Part

General. All haloboranes were prepared according to [5]. CH_2Cl_2 and MeCN were distilled over CaH_2 and stored over 4-Å molecular sieves. $EtN(i\text{-}Pr)_2$ was distilled over CaH_2 and directly used. NaI was dried *in vacuo* at 150° for 3 h. All glassware was oven-dried, cooled, and assembled under N_2. All of the experiments were carried out in a 100-ml round-bottom flask capped with a rubber septum, a magnetic stirring bar, and a connecting tube attached to a Hg bubbler under N_2. The experimental techniques used in handling air- and moisture-sensitive compounds have been described in [15]. The ^{1}H-, ^{11}B- and ^{13}C-NMR spectra were recorded on a *Varian Gemini-300* spectrometer with a *Nalorac-Quad* probe.

General Procedure for the Halogen-Exchange Reaction. Preparation of ChxBI$_2$·MeCN Complex. MeCN (5 ml) was added to $ChxBCl_2$ (990 mg, 6 mmol) at 0°. $ChxBCl_2$·MeCN was formed immediately as a white solid that dissolved in MeCN gradually. The ^{11}B-NMR spectrum showed a peak at δ 6 ppm. To this soln. was added 15 ml of a 1M soln. (2.5 equiv.) of NaI in MeCN at r.t., and the mixture was stirred at this temp. for 3 h when NaCl was separated. The ^{11}B-NMR spectrum showed a peak at δ 6 ppm. The solvent was pumped off when a solid mixture was obtained. $ChxBI_2$·MeCN was dissolved in CH_2Cl_2, and NaCl and NaI were removed by filtration. The salts were washed with CH_2Cl_2 (3×2 ml). The ^{11}B-NMR spectrum showed a peak at δ 8 ppm. Removal of CH_2Cl_2 gave $ChxBI_2$·MeCN as a solid.

Data of ChxBI$_2$·MeCN: ^{11}B-NMR (CH_2Cl_2): 8. ^{1}H-NMR ($CDCl_3$): 2.49 (*s*, 3 H); 1.88–0.80 (*m*, 11 H). ^{13}C-NMR ($CDCl_3$): 117.0; 28.5; 27.4; 26.8; 3.1. (It is usually difficult to observe the C-atom α to the B-atom in a ^{13}C-NMR spectrum due to rapid quadrapole-induced relaxation.)

General Procedure for the Enolboration and Aldolization. The above soln. of $ChxBI_2$·MeCN in CH_2Cl_2 was cooled to −78°, and the ketone (5 mmol) was added slowly. To this mixture, $EtN(i\text{-}Pr)_2$ (774 mg, 6 mmol) was added dropwise. The mixture was kept at −78° for 1 h. The ^{11}B-NMR spectrum of this mixture showed a peak at δ 41 ppm, revealing the completion of the reaction. The aldehyde (5 mmol) was then added dropwise at −78°, and the mixture was stirred for 3 h. The ^{11}B-NMR spectrum showed a peak at δ 31 ppm, indicating the formation of the boron aldolate. The mixture was then added to a phosphate buffer (pH 7) at r.t. and extracted with CH_2Cl_2 (3×20 ml). The combined org. soln. was concentrated. The residue was dissolved in Et_2O (20 ml), and MeOH (5 ml) was added. The soln. was cooled to 0°, aq. 30% H_2O_2 (3 ml) was added slowly, and the oxidation was continued for 3 h. The product was extracted with Et_2O (3×20 ml). The combined org. layer was washed with aq. $NaHCO_3$ (3×10 ml) and brine (3×10 ml), dried ($MgSO_4$), and concentrated. The regio- and diastereoselectivities were determined from the ^{1}H-NMR spectrum of the crude product and further proved by ^{1}H-NMR spectrum of the pure products obtained after a flash chromatography (SiO_2; hexanes/AcOEt 8:1).

syn-*1-Hydroxy-2-methyl-1-phenylpentan-3-one.* ^{1}H-NMR ($CDCl_3$): 7.40–7.20 (*m*, 5 H); 5.04 (*d*, J = 4.05, 1 H); 3.20–3.10 (OH); 2.84 (*dq*, J = 4.05, 7.14, 1 H); 2.58–2.26 (*m*, 2 H); 1.08 (*d*, J = 7.14, 3 H); 1.00 (*t*, J = 7.23, 3 H). ^{13}C-NMR ($CDCl_3$): 141.9; 128.3; 127.4; 126.0; 73.3; 52.3; 35.5; 10.6; 7.5.

syn-*5-Hydroxy-4,6-dimethylheptan-3-one.* ^{1}H-NMR ($CDCl_3$): 3.52 (*dd*, J = 2.97, 8.46, 1 H); 2.88–2.80 (OH); 2.74 (*dq*, J = 2.97, 7.23, 1 H); 2.65–2.42 (*m*, 2 H); 1.73–1.56 (*m*, 1 H); 1.12 (*d*, J = 7.23, 3 H); 1.06 (*t*, J =

7.26, 3 H); 1.01 (*d*, *J* = 6.51, 3 H); 0.86 (*d*, *J* = 6.84, 3 H). ^{13}C-NMR ($CDCl_3$): 76.3; 47.2; 34.9; 30.6; 19.07; 19.01; 9.6, 7.7.

syn-*5-Hydroxy-4-methylheptan-3-one*. ^{1}H-NMR ($CDCl_3$): 3.82 (*m*, 1 H); 2.75 (OH); 2.70 – 2.40 (*m*, 3 H); 1.61 – 1.30 (*m*, 2 H); 1.13 (*d*, *J* = 7.23, 3 H); 1.06 (*t*, *J* = 7.23, 3 H); 0.96 (*t*, *J* = 7.26, 3 H). ^{13}C-NMR ($CDCl_3$): 72.6; 49.3; 35.1; 26.9; 14.3; 10.5; 9.9; 7.6.

syn-*1-Hydroxy-2,4-dimethyl-1-phenylpentan-3-one*. ^{1}H-NMR ($CDCl_3$): 7.40 – 7.20 (*m*, 5 H); 5.00 (*d*, *J* = 3.84, 1 H); 3.15 (OH); 2.99 (*m*, 1 H); 2.60 (*m*, 1 H); 1.11 – 1.05 (*m*, 6 H); 0.99 (*d*, *J* = 6.90, 3 H). ^{13}C-NMR ($CDCl_3$): 141.9; 128.3; 127.5; 126.1; 73.6; 50.8; 40.7; 18.1; 17.8; 11.1.

syn-*3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one*. ^{1}H-NMR ($CDCl_3$): 8.00 – 7.90 (*m*, 2 H); 7.62 – 7.21 (*m*, 8 H); 5.25 (*d*, *J* = 2.34, 1 H); 3.75 – 3.60 (*m*, 2 H); 1.20 (*d*, *J* = 7.26, 3 H). ^{13}C-NMR: 205.8; 141.9; 135.7; 133.6; 128.8; 128.7; 128.5; 128.3; 127.4; 126.1; 73.1; 47.1; 11.2.

syn-*4-Hydroxy-3-methyl-1,4-diphenylbutan-2-one*. ^{1}H-NMR ($CDCl_3$): 7.40 – 7.20 (*m*, 8 H); 7.10 (*m*, 2 H); 4.97 (*d*, *J* = 3.84, 1 H); 3.64 (*s*, 2 H); 3.02 – 2.90 (*m*, 2 H); 1.09 (*d*, *J* = 7.14, 3 H). ^{13}C-NMR ($CDCl_3$): 212.8; 141.7; 133.5; 129.5; 128.8; 128.4; 127.5; 127.2; 126.0; 73.5; 51.7; 49.6; 10.9. EI-MS: 255 ($[M+1]^+$), 237, 149, 119, 107, 91, 57. Anal. calc. for $C_{17}H_{18}O_2$: C 80.31, H 7.09; found: C 80.17, H 7.17.

syn-*1-Hydroxy-1,2-diphenylpentan-3-one*. ^{1}H-NMR ($CDCl_3$): 7.40 – 7.16 (*m*, 10 H); 5.35 (*d*, *J* = 6.51, 1 H); 3.97 (*d*, *J* = 6.51, 1 H); 2.84 (OH); 2.44 – 2.28 (*m*, 1 H); 2.25 – 2.06 (*m*, 1 H); 0.86 (*t*, *J* = 7.23, 3 H). ^{13}C-NMR ($CDCl_3$): 211.5; 141.4; 134.3; 129.6; 128.7; 128.2; 128.1; 128.0; 127.9; 127.7; 126.6; 74.5; 65.8; 36.4; 7.6. EI-MS: 255 ($[M+1]^+$), 237, 205, 149, 107, 91, 57. Anal. calc. for $C_{17}H_{18}O_2$: C 80.31, H 7.09; found: C 80.22, H 7.01.

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