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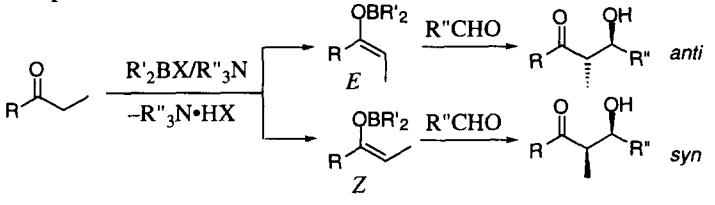
# *B,B*-Dihaloalkylboranes as Efficient Reagents for the Stereoselective Synthesis of *Syn*-Aldols[1]

**P. Veeraraghavan Ramachandran, Wei-chu Xu[2] and Herbert C. Brown***

*H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907-1393*

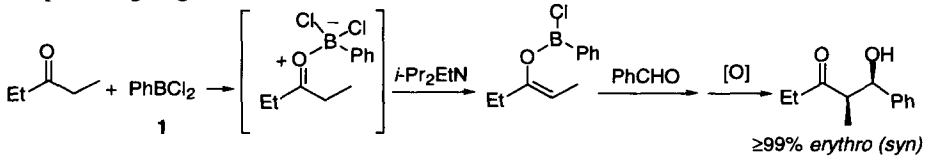
***Abstract:*** The easily synthesized *B,B*-dihaloalkylboranes, in the presence of either $Et_3N$ or *i*-$Pr_2NEt$, converts ethyl ketones, RCOEt, to 96-≥ 99% *Z*-enolates, converted by aldehydes to essentially pure *syn*-aldols. © 1997, Elsevier Science Ltd. All rights reserved.

Our investigations to understand the factors governing the stereoselective formation of *E*- or *Z*-enolborinates (providing *anti*- or *syn*-aldols, respectively) from ethyl ketones, using various $R_2BX$ reagents (X = Cl, Br, I, OMs, and OTf), with R of varying steric and electronic requirements, in the presence of a *tert*-amine, followed by reaction with an aldehyde (eq 1), led to several generalizations.[3] We had concluded that $R_2BX$ reagents, with lesser steric requirements of the R group, favor the formation of *Z*-enolborinates (providing *syn*-aldols), while those with larger R groups favor *E*-enolborinates (providing *anti*-aldols), On the other hand, reagents with better leaving groups, X = I and OTf, favor the formation of *Z*-enolborinates, whereas those with relatively poorer leaving groups favor *E*-enolborinates. While *tert*-amines of low steric requirements favor *E*-enolborinates, hindered amines favor the formation of *Z*-enolborinates. The effects of solvents, concentration, and temperature were also studied in detail.[3]




(1)

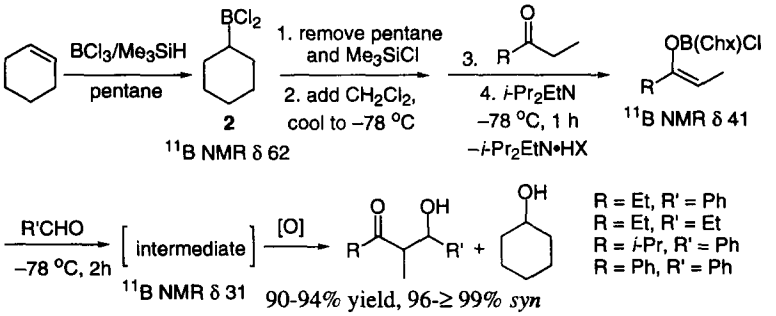
In contrast to the considerable attention given by us[3] and others[4] to enolboration studies using $R_2BX$ reagents over the past decade, there has been very little given to the corresponding $RBX_2$ reagents. In 1984, Hamana reported high *erythro (syn)*-selectivity in the aldol reaction of ethyl ketones with aldehydes using *B,B*-dichlorophenylborane (**1**) in the presence of a hindered amine, *N,N*-diisopropylethylamine (eq 2).[5] Although this reagent provides stereoselective formation of *Z*-enolates, it is surprizing that a search of the literature revealed only few reports of the applications of this reagent. For example, Evans applied **1** for the synthesis of Bafilomycin $A_1$[6a] and Koutek prepared a 7:3 *erythro-threo* mixture of sitophilure via enolboration of diethyl ketone.[6b] Morris used **1** to prepare *anti*-aldols from β-hydroxy ketones.[6c] It is possible that either the difficult preparation or the cost of the commercially available reagent might have been responsible for the lack of interest in this promising reagent.




(2)

In continuation of our studies on enolboration, we decided to examine the possibility that this behavior of $PhBCl_2$ might be general for $RBX_2$ reagents in enolboration, much like the study that we performed earlier for $R_2BX$ reagents. Recently, Soundararajan and Matteson reported an extremely efficient procedure for the preparation of *B,B*-dichlorocyclohexylborane (**2**) via the hydroboration of cyclohexene with dichloroborane generated *in situ* by the reaction of boron trichloride and trimethylsilane.[7] We tested **2** for the enolboration-aldolization of diethyl ketone under various reaction conditions and observed that irrespective of the conditions ≥99% *Z*-enolate is generated,[8] which upon treatment with benzaldehyde provides the *syn*-aldol exclusively. Our detailed study of the preparation of *syn*-aldols exclusively from ethyl ketones and aldehydes using various dihaloorganoboranes, all with varying steric and electronic environments, is reported in this *Letter*.

Hamana's typical procedure involved a sequential addition of **1** and a solution of the aldehyde in $CH_2Cl_2$ containing *i*-$Pr_2EtN$ to a stirred solution of the ketone in $CH_2Cl_2$ at –78 °C . This procedure was modified and optimized by Evans. We followed Evans' procedure for our study, since the former made it difficult to monitor the reaction by $^{11}B$ NMR spectroscopy. Accordingly, *i*-$Pr_2EtN$ was added to a flask containing **2** and 3-pentanone in $CH_2Cl_2$ at –78 °C. The enolboration was complete in 1 h. The $^{11}B$ NMR spectrum of an aliquot of the reaction mixture shifted from δ 62 ppm (singlet), corresponding to the reagent, to a singlet at δ 41 ppm, corresponding to an alkylchloroborinate. Following addition of benzaldehyde to the reaction mixture at –78 °C, the aldolate was produced. The $^{11}B$ NMR spectrum showed a singlet at δ 31 ppm.[9] This aspect provides a major advantage of this reagent over the dialkylboron reagents for enolboration. In the case of the latter reagents, the $^{11}B$ NMR spectrum of both of the enolborinate and aldolate intermediates show a singlet at δ 52 ppm, corresponding to a dialkylborinate, thereby precluding the possibility of monitoring the course of the reaction. Upon oxidation, the product aldol was obtained as ≥99% *syn* isomer, as established by the $^1H$ NMR spectrum (Scheme 1). We obtained ≤ 5% of the self-condensation product and ≥ 95% of the desired cross-aldol product, easily separated by column chromatography.




**Scheme 1**

Thus, we can prepare either *anti*- or *syn*-aldols respectively, using either $Chx_2BCl$[3] or $ChxBCl_2$ as the reagent for enolboration, both of which can be readily prepared from cyclohexene, $BCl_3$, and $Me_3SiH$.[7]

The effect of the experimental conditions on the reaction was examined. Changing the solvent had very little effect on the stereoselectivity (Table 1). However, the yield of the aldol is poor with THF as solvent. The reagent forms a strong complex ($^{11}B$ NMR δ 16 ppm) with THF and the amine either fails to liberate the reagent or to form the enolate at –78 °C.[10] When the reaction was allowed to warm to rt, the enolization was complete in 4 h, *al beit* with the formation of a considerable amount of self-condensation product. We prefer $CH_2Cl_2$ as the solvent. Warming the enolate to rt after its formation at –78 °C did not affect the stereoselectivity. The mode of addition of the reagent and substrates had little effect on the stereochemical outcome. These results are summarized in Table 1.

The effect of the aldehyde was tested by replacing benzaldehyde with propionaldehyde. Here also we observed the exclusive formation of the *syn*-aldol. The generality of **2** was examined by conducting the aldol reaction of a branched-chain ketone (2-methyl-3-pentanone) and an aralkyl ketone (propiophenone) with

benzaldehyde. In the case of 2-methyl-3-pentanone, the enolborinate was formed exclusively on the ethyl side (≥ 99% regioselectivity) and the product was predominantly (96%) *syn*-aldol.

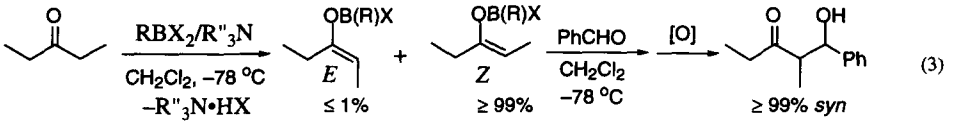
**Table 1. Enolboration-Aldolization with $ChxBCl_2$ Under a Range of Reaction Conditions**

| RCOEt R | amine | enolzn condn solvent | temp. °C | time[b] h | enolate[a] %Z | %E | R'CHO R' | aldolzn condn temp °C | time[b] h | yield isol. | aldol *syn*[c] % | *anti* % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Et | *i*-$Pr_2EtN$ | $CH_2Cl_2$ | −78 | 1 | ≥ 99 | ≤ 1 | Ph | −78 | 2 | 92 | ≥ 99 | ≤ 1 |
| Et | $Et_3N$ | $CH_2Cl_2$ | −78 | 1 | ≥ 99 | ≤ 1 | Ph | −78 | 2 | 88 | ≥ 99 | ≤ 1 |
| Et | *i*-$Pr_2EtN$ | $CH_2Cl_2$ | −78, 25 | 1, 0.5 | ≥ 99 | ≤ 1 | Ph | −78 | 2 | 91 | ≥ 99 | ≤ 1 |
| Et | *i*-$Pr_2EtN$ | pentane | −78 | 1 | ≥ 99 | ≤ 1 | Ph | −78 | 2 | 85 | ≥ 99 | ≤ 1 |
| Et | *i*-$Pr_2EtN$ | EE | −78 | 1 | ≥ 99 | ≤ 1 | Ph | −78 | 2 | 93 | ≥ 99 | ≤ 1 |
| Et | *i*-$Pr_2EtN$ | THF | 25 | 4 | ≥ 99 | ≤ 1 | Ph | −78 | 2 | 31 | ≥ 99 | ≤ 1 |
| Et | *i*-$Pr_2EtN$ | $CH_2Cl_2$ | −78 | 1 | ≥ 99 | ≤ 1 | Et | −78 | 2 | 94 | ≥ 99 | ≤ 1 |
| *i*-Pr | *i*-$Pr_2EtN$ | $CH_2Cl_2$ | −78 | 1 | 96 | 4 | Ph | −78 | 2 | 90 | 96 | 4 |
| Ph | *i*-$Pr_2EtN$ | $CH_2Cl_2$ | −78 | 1 | ≥ 99 | ≤ 1 | Ph | −78 | 2 | 93 | ≥ 99 | ≤ 1 |

[a]The *Z*/*E* ratio is based on the *syn*/*anti* ratio, ref. 8. [b]Determined by $^{11}B$ NMR spectroscopy. [c]The *syn*/*anti* ratio is determined on the basis of $^1H$ NMR.

The effect of the steric requirements of the alkyl group of $RBCl_2$ was tested by carrying out the enolboration-aldolization with the commercially available (Aldrich) *B,B*-dichloro-*n*-butylborane (**3**). The result is very similar to that obtained with **2** (eq 3). We prepared *B,B*-dichlorothexylborane (**4**) from 2,3-dimethyl-2-butene using the Matteson procedure described before[7] and this reagent also provided the *syn*-aldol exclusively from diethyl ketone and benzaldehyde (eq 3).

The effect of the halogen atoms was tested using *B,B*-dibromocyclohexylborane (**5**), prepared via the trimethylsilane procedure,[7] for the enolboration of diethyl ketone, followed by aldolization with benzaldehyde. We observed that the enolboration was complete within 1 h ($^{11}B$ NMR δ 41 ppm) and the aldolization was complete within 2 h ($^{11}B$ NMR δ 31 ppm). Alkaline $H_2O_2$ oxidation provided the aldol, the analysis of which by $^1H$ NMR revealed it to be ≥ 99% *syn* (eq 3). The results are summarized in Table 2.




(3)

**3**, R = *n*-Bu, X = Cl; **4**, R = Thx, X = Cl; **5**, R = Chx, X = Br

**Table 2. Enolboration-Aldolization of Diethyl Ketone/Benzaldehyde with $RBX_2$ Reagents Under Standard Conditions**

| compd | $RBX_2$ R | X | amine | enolzn condn solvent | temp °C | time[b] h | enolate[a] %Z | %E | aldolzn condn temp °C | time[b] h | yield isol. | aldol *syn*[c] % | *anti* % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1**[d] | Ph | Cl | *i*-$Pr_2EtN$ | $CH_2Cl_2$ | −78 | 1 | ≥99 | ≤1 | −78 | 2 | ≥ 99 | ≥ 99 | ≤ 1 |
| **2** | Chx | Cl | *i*-$Pr_2EtN$ | $CH_2Cl_2$ | −78 | 1 | ≥99 | ≤1 | −78 | 2 | 92 | ≥ 99 | ≤ 1 |
| **3** | *n*-Bu | Cl | *i*-$Pr_2EtN$ | $CH_2Cl_2$ | −78 | 1 | ≥99 | ≤1 | −78 | 2 | 92 | ≥ 99 | ≤ 1 |
| **4** | Thx | Cl | *i*-$Pr_2EtN$ | $CH_2Cl_2$ | −78 | 1 | ≥99 | ≤1 | −78 | 2 | 88 | ≥ 99 | ≤ 1 |
| **5** | Chx | Br | *i*-$Pr_2EtN$ | $CH_2Cl_2$ | −78 | 1 | ≥99 | ≤1 | −78 | 2 | 83 | ≥ 99 | ≤ 1 |

[a]The *Z*/*E* ratio is based on the *syn*/*anti* ratio, ref. 8. [b]Determined by $^{11}B$ NMR spectroscopy. [c]The *syn*/*anti* ratio is determined on the basis of $^1H$ NMR. [d]From ref. 5.

All of the above results make the *B,B*-dihaloalkylborane reagents superior to all of the earlier reagents reported for the formation of *Z*-enolborinates (*syn*-aldols). The currently used dialkylboron triflate reagents do not always provide the *syn*-aldols exclusively.[4] Moreover, they are relatively unstable and may have to be

freshly prepared. As part of an unrelated project, we have observed that neat alkyldihaloboranes can be stored under nitrogen without deterioration for several months.[11]

In conclusion, we have extended the observation made by Hamana using *B,B*-dichlorophenylborane and have shown that all of the *B,B*-dihaloalkylboranes (**2-5**) of varying steric and electronic environments examined can be conveniently applied to synthesize *syn*-aldols from ethyl ketones under different experimental conditions, such as varying the amines, the solvents, and the temperatures. Unlike the reaction of $R_2BX$ reagents, the reactions with $RBX_2$ reagents can be easily monitored using $^{11}B$ NMR spectroscopy. The simple preparation using the Matteson procedure, the stability of these reagents, the simple reaction conditions,[12] and the exclusive regio- and stereoselectivity of the products obtained, all make this procedure very attractive for the synthesis of *syn*-aldols.

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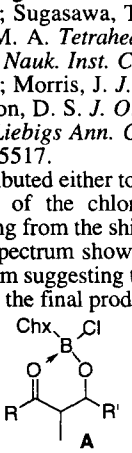
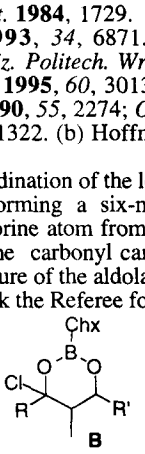
9. The δ 31 peak could be attributed either to a weak coordination of the lone pair of the carbonyl oxygen of the aldolate to the boron of the chloroborinate, forming a six-membered chelate (**A**) or an α-chloroalkoxyboronate arising from the shift of the chlorine atom from the boron to the carbonyl carbon atom (**B**). The $^{13}C$ NMR spectrum showed none of the carbonyl carbon, but a peak corresponding to the $sp^3$ carbon at δ 104.4 ppm suggesting that the structure of the aldolate intermediate may be **B**. Either intermediate would provide the final product. We thank the Referee for bringing this to our attention.



**A**



**B**

10. The reagent **2** complexes strongly with EE ($^{11}B$ NMR δ 18 ppm). However, the reagent is released by the amine for enolborations. The reagent also forms strong complexes with both of the trialkylamines used, $Et_3N$ and *i*-$Pr_2EtN$ ($^{11}B$ NMR δ 13 ppm).
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12. All of the operations were carried out under nitrogen.[13] An oven-dried, 50 mL round-bottom flask equipped with a side-arm, magnetic stirring bar, and a connecting tube was cooled to rt in a stream of nitrogen. $ChxBCl_2$ (1.0 g, 6 mmol) and $CH_2Cl_2$ (30 mL) were added via a cannula to the flask, followed by the addition of 3-pentanone (0.43 g, 5 mmol). The flask was cooled to –78 °C and *i*-$Pr_2EtN$ (0.87 g, 6.5 mmol) was added using a syringe. The enolborinate was generated instantaneously with concurrent formation of *i*-$Pr_2EtN$•HCl. The $^{11}B$ NMR spectrum of an aliquot showed a singlet at δ 41. The mixture was stirred at this temperature for 1 h. PhCHO was added to this mixture and the reaction was followed using $^{11}B$ NMR spectroscopy of an aliquot. Upon completion of the reaction ($^{11}B$ NMR δ 31) methanol (8 mL) was added to the mixture, and oxidized with alkaline $H_2O_2$. The crude product was extracted with $CH_2Cl_2$, concentrated, chromatographed through silica (hexane:ethyl acetate, 10:1), and the solvents were removed to obtain (0.89 g) 92% of 2-methyl-3-oxo-1-phenylpentanol. The structure was confirmed by $^1H$ and $^{13}C$ NMR spectroscopy. The *syn/anti* ratio was determined from the $^1H$ NMR spectrum.
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