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B,B-Dihaloterpenylboranes as reagents for the diastereo- and enantioselective synthesis of *syn*-aldols

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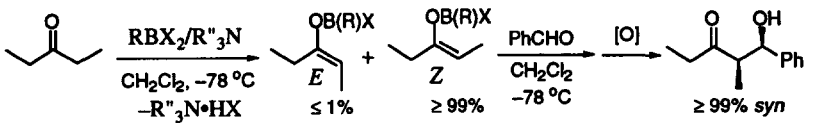
Abstract: A series of known and new *B,B*-dihaloterpenylboranes, readily synthesized from the corresponding terpenes, were examined for the diastereo- and enantioselective synthesis of *syn*-aldols. Thus, $IpcBCl_2$, $EapBCl_2$, $LgfBCl_2$, *cis*-$MyrBCl_2$, 2-$IcrBCl_2$, 4-$IcrBCl_2$, and 2-$IcrBBr_2$ in the presence of *i*-Pr_2NEt, convert 3-pentanone to ≥99% *Z*-enolates, converted by aldehydes to pure *syn*-aldols in 7–74% enantiomeric excess (ee). The most efficient of these reagents, *B,B*-dibromo-2-isocaranylborane, was tested for the enolboration of 3-pentanone, followed by aldolization with a series of aldehydes. © 1997 Elsevier Science Ltd

The diastereoselective syntheses of cross aldols via enolboration of ketones have been essentially mastered over the past two decades.[1] Although most of the literature reports on enolborations utilize R_2BX (X=Cl, Br, I, OTf, etc.) reagents,[1] there have been only scanty reports involving the corresponding RBX_2 reagents.[2] As part of our ongoing projects on enolboration, we recently reported the utilization of *B,B*-dihalomonoalkylboranes as reagents for the stereoselective enolization of ethyl ketones, followed by *syn*-selective aldolization with a representative series of aldehydes (Eq. 1).[3] All of the reagents tested provided the *syn*-aldols selectively.



(1)

R = *n*-Bu, Chx, Ph, Thx; X = Cl, Br

Enantioselective aldol reactions have been achieved by way of substrate- and/or reagent-controlled enolborations.[4] The reagents that have been developed for the latter strategy include several R_2BX derivatives prepared from terpenes, such as α-pinene,[5] carene,[6] and menthene.[7] However, to the best of our knowledge, there has been no report of the utilization of dihaloborane derivatives, with an optically active alkyl group attached, for enantioselective enolboration–aldolization. Encouraged by our earlier success with the RBX_2 reagents (Eq. 1),[3] we undertook a study of the enolboration of ethyl ketones with a series of chiral dihaloborane reagents (**1–6**) prepared from readily available terpenes employing the BCl_3–Me_3SiH procedure developed by Soundararajan and Matteson.[8] Promising preliminary results are reported herein.

It has been recorded, in the case of Ipc_2BX reagents, that the isopinocampheyl (Ipc) moiety usually provides high enantioselectivity for *syn*-selective, and low enantioselectivity for *anti*-selective aldol reactions.[5] For example, while diisopinocampheylboron triflate generally provides high enantiomeric excess (ee) for *syn*-aldols, diisopinocampheylboron chloride affords poor ee for *anti*-aldols. We were

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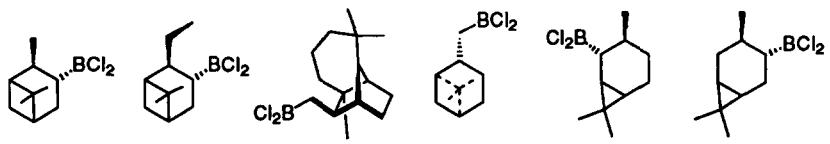
Table 1. Enolboration–aldolization of diethyl ketone/benzaldehyde with $TerBCl_2$ reagents under standard conditions

reagent	R^*BCl_2 R^*	enolate[a] %Z	%E	yield isol.	aldol[b] *syn*[c] %	*anti* %	ee[d] %	config.[d]
1	Ipc	≥99	≤1	88	≥99	≤1	15	*1R,2R*
2	Eap	≥99	≤1	92	≥99	≤1	19	*1R,2R*
3	Lgf	≥99	≤1	95	≥99	≤1	8	*1S,2S*
4	Myr	≥99	≤1	90	≥99	≤1	7	*1S,2S*
5	2-Icr	≥99	≤1	93	≥99	≤1	59	*1R,2R*
6	4-Icr	≥99	≤1	98	≥99	≤1	28	*1S,2S*

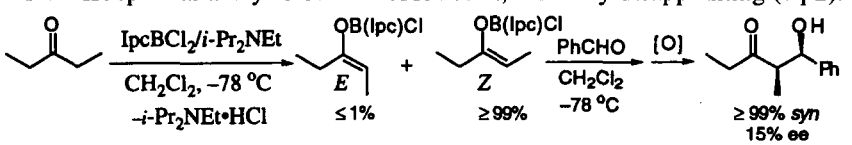
[a]The enolization was carried out in CH_2Cl_2 at −78 °C for 1 h. The *Z/E* ratio is based on the *syn/anti* ratio of the aldol. [b]The aldolization was carried out at −78 °C for 2 h. [c]The *syn/anti* ratio is determined on the basis of ^1H NMR. [d]Determined by ^1H and ^{19}F NMR of the corresponding MTPA derivative.

curious to examine this 'super chiral auxiliary',[9] α-pinene, for *syn*-selective aldol reactions under the changed steric and electronic environments.



1 (−)-$IpcBCl_2$ **2** (−)-$EapBCl_2$ **3** (−)-$LgfBCl_2$ **4** (+)-$MyrBCl_2$ **5** (−)-2-$IcrBCl_2$ **6** (−)-4-$IcrBCl_2$

i-Pr_2EtN was added to a flask containing isopinocampheyldichloroborane ($IpcBCl_2$, **1**) 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 within 2 h (^{11}B NMR δ 31 ppm).[3] Upon oxidation, the product aldol was obtained as ≥99% *syn* isomer, as established by the ^1H NMR spectrum. Since all of the dihaloboranes consistently yield *syn*-aldols, the diastereoselectivity achieved with this reagent is not surprizing. However, the enantiomeric excess (ee) realized, 15% as determined by the ^{19}F NMR spectral analysis of the MTPA ester,[10] is very disappointing (eq 2).



(2)

In our asymmetric reduction program, we observed that increasing the steric requirements at the 2-position of the apopinene moiety in the reagent containing such a group results in a considerable increase in the ee of the product alcohols produced.[11] On this basis, we examined $EapBCl_2$ (**2**) for the enolboration–aldolization of 3-pentanone-benzaldehyde. The modest improvement in ee achieved (19%) fell short of our expectations. We then investigated reagents **3**–**6**. The reagents **3** and **4** derived from the terpenes containing terminal olefins, viz. longifolene and β-pinene, yielded poor enantioselectivity (7–8% ee). This may be due to the fact that the nearest chiral center is one carbon removed from the boron atom.

Our experiences in the allyl- and crotylboration program suggested that the reagents derived from the two carenes might prove superior than those derived from α-pinene.[12] Indeed reagents **5** and **6** offered reasonably good ee for the aldol. The results on the enolboration–aldolization of 3-pentanone-benzaldehyde with $TerBCl_2$ reagents are summarized in Table 1.

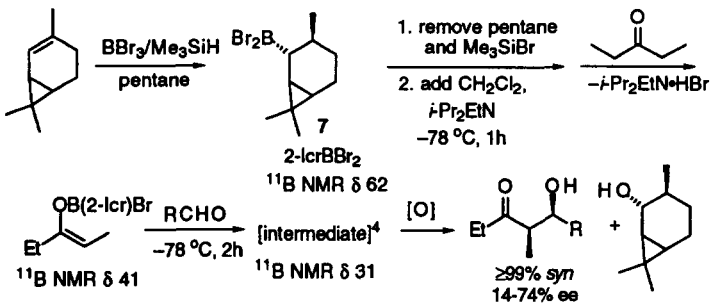
Since 2-$IcrBCl_2$ provided the best results, the corresponding dibromoborane (2-$IcrBBr_2$, **7**) was prepared from 2-carene and examined for the same reaction (Scheme 1). This reagent provides improved enantioselectivity (74% ee) for the product aldol. We investigated the generality of this

Table 2. Enolboration–aldolization of diethyl ketone/RCHO with 2-IcrBBr$_2$ (**7**) under standard conditions

RCHO R	enolate[a] %*Z*	%*E*	yield isol.	aldol[b] *syn*[c] %	*anti* %	ee[d] %	config.[d]
Ph	≥99	≤1	88	≥99	≤1	74	*1R,2R*
Et	≥99	≤1	92	≥99	≤1	59	*1S,2R*
i-Pr	≥99	≤1	93	≥99	≤1	58	*1S,2R*
t-Bu	≥99	≤1	98	≥99	≤1	14	*1R,2R*

[a–d]See footnotes *a-d* in Table 1.

reagent by carrying out the cross aldol reaction with a representative series of aldehydes and obtained 14–74% ee for the products. The aldols from unhindered aliphatic aldehydes were obtained in 58–59% ee. When the aldehyde was hindered, the ee dropped considerably. For example, the reaction of pivalaldehyde with the corresponding enolate from 3-pentanone, affords only 14% ee. The results are summarized in Table 2.



Scheme 1.

In conclusion, we have synthesized a series of *B,B*-dihaloterpenylboranes and examined them for enantioselective aldol reactions. One of these *B,B*-dibromo-2-isocaranylborane appears to be a very promising reagent.[13,14] We are continuing the investigations on the scope of this reagent. We are also examining these and several new R*BX$_2$ reagents for asymmetric aldolizations.

Acknowledgements

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13. All of the operations were carried out under nitrogen.[14] 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. 2-IcrBBr$_2$ (1.9 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·HBr. 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 aliquots. 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 (1*R*,2*R*)-2-methyl-3-oxo-1-phenylpentanol. The structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The *syn*/*anti* ratio was determined from the ^{1}H NMR spectrum. The % ee and configuration were determined by analysis of the ^{19}F NMR spectrum of the MTPA ester.
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