Pergamon

Tetrahedron Letters, Vol. 37, No. 46, pp. 8345-8348, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01908-9

A General, Efficient, Convenient Synthesis of Chiral Bis(Terpenyl)haloborane Reagents, Valuable for Asymmetric Synthesis *via* Organoboranes

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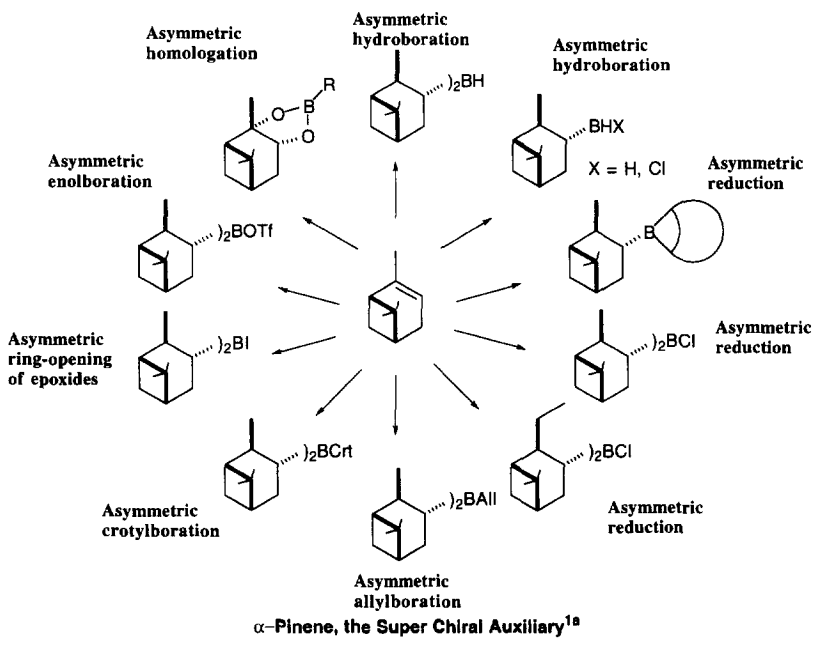
Abstract: The chiral, sterically-varied bis(terpenyl)haloboranes (Ter_2BX; X = Cl, Br, and I), potentially important reagents for asymmetric synthesis, are conveniently prepared in essentially quantitative yield by the in situ tandem reduction-hydroboration under mild conditions of boron trihalide, trialkylsilane, and representative terpenes (Ter). Use of ethyl ether (EE) as solvent accelerates the formation of the sterically bulkier Ter_2BCl derivatives. Typically the reaction is over in less than 2 h in comparison with the literature procedure requiring 36 h at room temperature. Copyright © 1996 Published by Elsevier Science Ltd

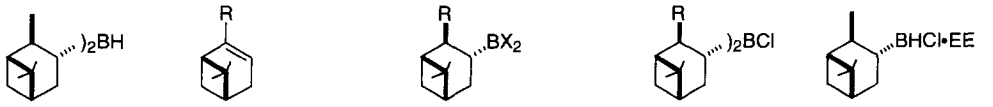
In the past decade we have been exploring asymmetric synthesis *via* chiral organoboranes derived from terpenes.[1] As a result, a variety of procedures have become available for the enantioselective synthesis of chiral organoboranes *via* asymmetric hydroboration using α–pinene derived borane reagents.[1] We have successfully utilized these reagents in achieving high enantioselectivity, not only in asymmetric hydroboration, but also in asymmetric reduction, allylboration, crotylboration, and opening of *meso*-epoxides.[1] Thus, with the advent of this promising chemistry, a number of reagents have been synthesized for achieving high enantiomeric excess (ee) in compounds produced *via* terpene based borane reagents (Chart 1).[1]

Chart 1



We have been pursuing research to find improved steric and electronic matches between the reagent, derived from terpenes, and the substrate, thereby achieving higher enantioselectivity in their reactions. To this end, we have synthesized sterically-varied α–pinene derivatives (2-organylapopinenes, 2-R-apopinenes, 2-Rap derivatives, **2a-f**)[2] and, have transformed them into valuable borane reagents, applicable for asymmetric synthesis *via* organoboranes (Chart 2).

Chart 2

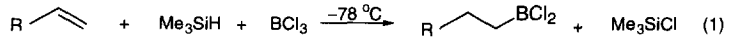


1 **2a** R = Me **2d** R = *i*-Bu **2b** R = Et **2e** R = Ph **2c** R = Pr **2f** R = *i*-Pr **3** X = H, $RapBH_2$ **4** $RapBX_2$, X = Cl, Br, I **5** R = Me **6** R = Et **7** R = $(CH_2)_2Cl$ **8** IpcBHCl•EE

For example, enantiomerically pure borane reagents (**3b,f**) derived from 2-ethyl- (**2b**)[2a] and 2-isopropylapopinenes (**2f**),[3] respectively, provide moderate to excellent results in the asymmetric hydroboration of prochiral alkenes. Moreover, the reducing agent, Eap_2BCl (**6**), derived from 2-ethylapopinene (**2b**), provides excellent results for the asymmetric reduction of certain prochiral ketones, far better than those realized with the corresponding Ipc_2BCl.[4] A slight modification of 2-ethylapopinene to 2-β-chloroethylapopinene provides a further improved dialkylchloroborane reagent (**7**), one that achieves even better results for the asymmetric reduction of several classes of prochiral ketones than are realized with reagents **5** and **6**.[5] Recently, we synthesized the isopinocampheylchloroborane reagent (IpcBHCl, **8**) from the corresponding $IpcBH_2$ (**3a**) or $IpcBCl_2$ (**4a**) reagents, and demonstrated its efficacy for the asymmetric cyclic hydroboration of 1-allyl-1-cyclohexene to achieve the synthesis of the *trans*-1-decalone in ≥99% ee.[6]

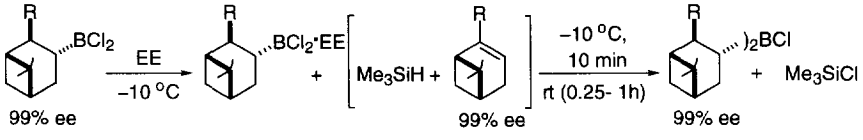
Although, these reagents have been made and utilized for asymmetric synthesis, there remains considerable opportunity to improve further the ee of the chiral compounds produced *via* the asymmetric reduction and opening of *meso*-epoxides. During the course of our research in the area of asymmetric synthesis *via* organoboranes, we have been attempting to improve the literature procedures to achieve convenient and efficient syntheses of such chiral borane reagents in optically pure form.[7] Thus, for the better understanding of the chemistry of these reagents, obtained from structurally varied 2-organylapopinenes (2-R-apopinenes, **2a-f**) and certain representative terpenes (Ter), for asymmetric synthesis requires a simple, general, efficient procedure for preparing the bis(2-organylapoisopinocampheyl)haloboranes (Rap_2BX; X = Cl, Br, and I) reagents. Thus, we wish to report in this communication a general, convenient , efficient one-pot procedure for the preparation of chiral sterically-varied, Rap_2BX (X = Cl, Br, and I), as well as other Ter_2BX, from readily available terpenes, providing potentially important reagents for asymmetric synthesis.

Recently, we prepared structurally varied 2-R-apopinenes (**2a-f**), and converted them into chiral hydroborating agents *via* commercially available boranes and systematically investigated their hydroboration characteristics.[2d] We also reported a convenient method for upgrading the 2-R-apopinenes (**2a-f**) to high ee.[8] Soundararajan and Matteson reported the reduction of boron trichloride with trialkylsilane at −78 °C in the presence of alkene, either in pentane or under neat conditions, to provide the formation of a small equilibrium concentration of $BHCl_2$, trapped by alkene already present to give the organyldichloroborane (eq 1).[9]



We then systematically extended this methodology for the synthesis of (2-organyl-apoisopinocampheyl)dihaloboranes ($RapBX_2$, X = Cl, Br and I, except for $IpcBI_2$) from the corresponding 2-R-apopinenes.[7d] In our recent publication,[10] we demonstrated that the reduction of alkylchloroborane, such as $IpcBCl_2$ (**4a**), with trimethylsilane is highly accelerated in EE as solvent to provide IpcBHCl·EE (**8**), a major component of the reaction, in less than 5 minutes. Encouraged by this result, we explored the synthesis of optically pure Rap_2BCl in EE by this procedure. The enantiomerically pure $RapBCl_2$ reagents (**4a-e**) were made according to the literature procedure.[7d] Thus, to the cold (−10 °C) EE (10 mL) as solvent, $IpcBCl_2$ (10 mmol) was added slowly, followed by a solution of a mixture of liquid trimethylsilane (10 mmol), previously condensed at −78 °C, and α−pinene (**2a**, 11 mmol). The reaction, monitored by ^{11}B NMR (δ 77-80) spectroscopy, was over in less than 15 min! The evaporation of volatiles at room temperature under reduced pressure (10 mmHg, 30 min and 0.5 mmHg, 1 h) provided a quantitative formation of the desired Ipc_2BCl. Under similar conditions, the sterically demanding Rap_2BCl (R = Et, Pr, *i*-Bu and Ph) of ≥99% ee were prepared in about 0.25-1 h at room temperature (25 °C) in quantitative yields (Scheme 1).

Scheme 1

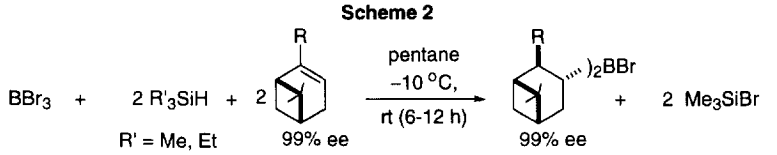


R = Me, Et, Pr, *i*-Bu, and Ph

The chemical and optical purities of Rap_2BCl are determined by ^1H and ^{13}C NMR spectra of the resultant alcohol obtained after alkaline peroxide oxidation of Rap_2BCl and by the analysis of the menthyl carbonate derivatives of the alcohols by capillary GC (SPB-5 column).[7d]

Synthesis of Rap_2BBr (R = Me, Br) is achieved in excellent yield in 1.5-2.0 h room temperature, albeit with slow cleavage of EE, ~5%.[11] Therefore, this reaction was successfully tried in a non-ethereal solvent, such as pentane. Thus, to the cold solution (−10 °C) of BBr_3 in pentane (1.0 *M*, 10 mmol) are added a mixture of α−pinene (**2a**, 23 mmol) and either trimethylsilane or triethylsilane (20 mmol). The desired Rap_2BBr compounds (^{11}B NMR signal at δ 79-81) are obtained in quantitative yields in 6-12 h at room temperature (Scheme 2).

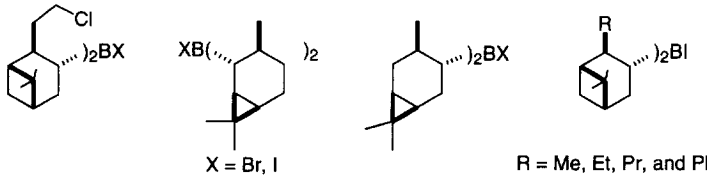
Scheme 2



R = Me, Et, Pr, *i*-Bu, and Ph

Under similar conditions 2-R-apopinenes (**2b-e**) and 2- and 3-carenes are conveniently converted into chiral diterpenylbromo- and -iodoboranes (Ter_2BX, X = Br, I) in quantitative yield. The desired diterpenyliodoboranes are formed in less than 5 min at 0 °C (by ^{11}B NMR spectra). These examples are shown in Chart 3.

Chart 3



In conclusion, we have successfully demonstrated the utility of the reaction of $RapBCl_2$ with trimethylsilane in EE for a rapid one-pot synthesis of Rap_2BCl, with sterically-varied R groups, potentially useful borane reagents for asymmetric synthesis *via* organoboranes. This methodology can be utilized in non-ethereal solvents, such as pentane, in the case of the more reactive derivatives of Ter_2BX, X = Br or I. For these derivatives the reactions are complete in a relatively short time. We are currently investigating the applicability of these organoborane reagents in asymmetric synthesis. Our preliminary investigation of the opening of representative examples of *meso*-epoxides with Eap_2BBr reveals remarkably improved enantioselectivities in the reaction.[12]

Acknowledgment. This work was initiated with support from the National Institutes of Health and completed with support from the Borane Research Fund.

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(*Received in USA* 30 *August* 1996; *accepted* 20 *September* 1996)