

Asymmetric synthesis with the robust and versatile 10-substituted 9-borabicyclo[3.3.2]decanes: Homoallylic amines from aldimines*

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Abstract: The asymmetric allylboration of *N*-H aldimines, generated from either *N*-trimethylsilyl or *N*-diisobutylalanyl precursors, with *B*-allyl-9-borabicyclo[3.3.2]decane is described. The desired homoallylic amines are obtained efficiently (60–90 %) and selectively (60–89 % ee). A non-oxidative work-up procedure has also been developed for this new method, which permits the recovery of the air-stable pseudoephedrine (PE) complex (50–70 %), which is conveniently converted back to *B*-allyl-9-borabicyclo[3.3.2]decane (98 %) with allylmagnesium bromide in ether for its reuse in the asymmetric allylboration process. Additional studies were conducted to better understand these processes and the origin of the observed enantioselectivity.

Keywords: organoboranes; allylboration; aldimines; homoallylic amines; borabicyclo[3.3.2]decanes.

INTRODUCTION

The asymmetric synthesis of homoallylic amines through the 1,2-addition of allylmetals to imines is an important process and one that has undergone continual development in recent years [1]. While numerous organometallic reagents have been developed for the asymmetric allylation of imines, the efficacy of organoboranes in this regard has been known since the early studies of Yamamoto et al. who found high diastereoselectivities in the addition of *B*-allyl-9-BBN to chiral imines [2]. The asymmetric allylboration of achiral imines with the chiral borane reagent, allyldiisopinocampheylborane (AlIB(Ipc)₂) was first reported by Itsuno [3]. In these studies, it was thought that the reagent added to either *N*-trimethylsilyl (*N*-TMS) or *N*-diisobutylalanyl (*N*-DIBAL) imines to afford the corresponding homoallylic amine **6** with good enantioselectivity (e.g., PhHC = NTMS, 73 % ee). However, this reactivity was later questioned by Brown and coworkers who discovered that the *N*-TMS imines were actually unreactive toward AlIB(Ipc)₂ and that it was the *N*-H imine which formed upon aqueous work-up that was the reacting species [4]. Thus, with the addition of water (1 equiv) to the *N*-TMS imine/AlIB(Ipc)₂ mixture at –78 °C, significantly higher enantioselectivities were observed (e.g., PhHC = NTMS (PhHC = NH), 92 % ee) (Fig. 1).

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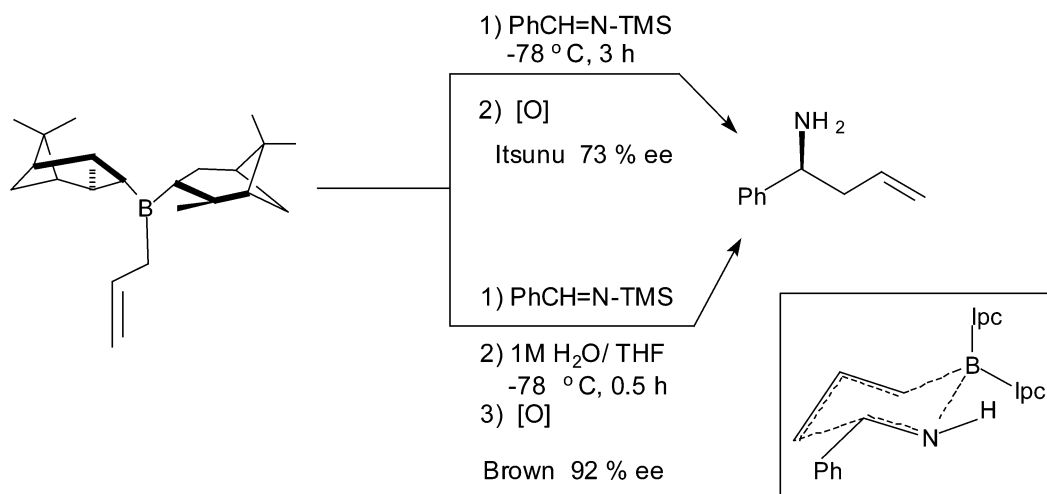


Fig. 1 Asymmetric allylboration of aldimines with allyldiisopinocampheylborane.

Recently, we described the preparation of both enantiomers of *B*-allyl-10-trimethylsilyl-9-bora-bicyclo[3.3.2]decane (*B*-All-10-TMS-9-BBD, **1**) and its use in the highly enantioselective allylation of aldehydes [5]. The *B*-crotyl, and -allenyl systems have also been described, and these reagents also add rapidly and highly selectively to representative aldehydes at $-78\text{ }^{\circ}\text{C}$ to produce the corresponding β -methylhomoallylic and homopropargylic alcohols [5,6]. The γ -TMS-propargyl-10-TMS-9-BBD reagent was also prepared, which provides a highly efficient route to α -allenyl carbinols with excellent enantioselectivity [7]. The BBD system can be easily modified to accommodate ketone substrates and, in general, has several advantages over the more established $\text{B}(\text{Ipc})_2$ reagents in that they are more stable and are easier to use [8]. They also exhibit less sensitivity to reaction temperatures and the presence of magnesium salts than are the $\text{B}(\text{Ipc})_2$ reagents [9]. However, perhaps the most meritorious feature of the BBD reagents is the clean conversion of their air-stable crystalline pseudoephedrine (PE) complexes to the corresponding borane reagents through simple Grignard procedures. Other derivatives of the BBD system such as *B*-MeO-10-TMS-9-BBD are also essentially air-stable and can be purified by distillation. These properties can be contrasted to far more operationally difficult handling and manipulation of the air-sensitive $\text{XB}(\text{Ipc})_2$ ($\text{X} = \text{OMe}, \text{Cl}$) precursors to the corresponding organoborane reagents. Moreover, any oxidation of these precursors results in reagents which give significantly lower product ee's [10]. Since these impure precursors are thermally unstable to distillation, they cannot be easily converted back to useable reagents. The BBD reagents generally exhibit selectivities which equal or exceed those of the $\text{B}(\text{Ipc})_2$ reagents [5,7]. We felt that it was important to examine the asymmetric allylation of aldimines with the BBD reagents **1** to both provide alternatives to the existing systems and to better understand this important process.

SYNTHESIS OF THE ALLYLBORANES **1**

Recently, we discovered that the stable, commercially available TMSCHN_2 undergoes the clean insertion of CHTMS into a ring B-C bond in *B*-R-9-BBNs [5]. Fortunately, this process (10 h, C_6H_{14} , $70\text{ }^{\circ}\text{C}$) is also successful for **2**, affording the thermally stable *B*-MeO-10-TMS-9-BBD (**3**) in 97 % yield after distillation (bp $80\text{ }^{\circ}\text{C}$, 0.10 mm Hg) (Scheme 1). The borinic ester **3** is also stable to the open atmosphere for brief periods of time (17 h, 3 % oxidation), in marked contrast to **2** and $\text{MeOB}(\text{Ipc})_2$. Moreover, **3** is readily converted to (\pm)-**1** with allylmagnesium bromide ($\text{AlI}(\text{MgBr})$) in ether (98 %).

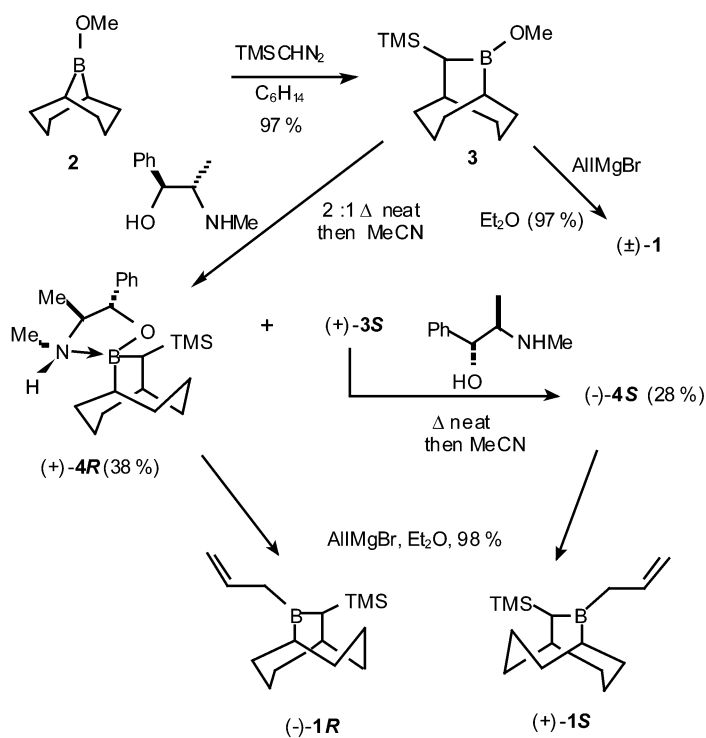


Fig. 2 Preparation of the *B*-allyl-10-trimethylsilyl-9-borabicyclo[3.3.2]boranes **1**.

Employing a modified version of the Masamune resolution protocol [11], $(\pm)\text{-3}$ was added to 0.5 equiv of $(1S,2S)\text{-PE}$ in MeCN which gave a 38% yield of $(+)\text{-4R}$ as a pure crystalline compound leaving $(-)\text{-3R}$ in solution. After concentration of the supernatant to remove the liberated MeOH, 0.5 equiv of $(1R,2R)\text{-PE}$ was added to a fresh solution of the residue in acetonitrile, ultimately giving a 28% yield of the pure crystalline $(-)\text{-4S}$. Reversing this order gives first, $(-)\text{-4S}$, and second, $(+)\text{-4R}$, also in a 66% combined total yield of enantiomerically pure forms of **4** from $(\pm)\text{-3}$! These complexes are air-stable and can be stored indefinitely. The complex $(+)\text{-4R}$ is wholly chelated in the solid state, while, in solution, **4** exists in both the open and closed forms (^{11}B NMR (C_6D_6) δ 56.3, 23.7) [5].

The direct conversion of **4** to **1** was accomplished with AllMgBr in Et_2O , the metathesis proceeding very cleanly at -78°C . The stable allylboranes **1** can be isolated (98%) in chemically and optically pure form through simple filtration through Celite under N_2 to remove the Mg^{2+} salts followed by concentration in vacuo. Under N_2 , **1** is stable for weeks at 25°C . The ease and efficiency of the preparation of both enantiomers of **1** from **2** in 63% overall yield is greatly enhanced by the air-stability of its precursor, **4**, which largely avoids many of the difficulties usually associated with dialkylborane reagents.

ASYMMETRIC ALLYLATION OF ALDIMINES WITH **1**

As discussed above, Brown had noted that *N*-TMS imines failed to react significantly with $\text{AllB}(\text{Ipc})_2$ [4]. This had led to his identification of the corresponding *N*-H imine as the actual reacting species. Because the enantioselectivities observed with allylations employing $\text{AllB}(\text{Ipc})_2$ are known to be highly temperature-dependent [9b], the hydrolysis of the *N*-TMS and *N*-DIBAL were conducted at -78°C , which increased the observed ee compared to earlier work where the hydrolysis had occurred at ambi-

ent temperatures [4]. With *N*-TMS benzaldimine, no reaction takes place with **1** even after one week at 25 °C! Similarly, with *N*-DIBAL benzaldimine, no reaction takes place with **1** after one day at 25 °C. However, upon the addition of 1.0 equiv of methanol to these mixtures at -78 °C, allylation is complete in <1 h, with both giving the expected homoallylic amine **6a** with virtually identical selectivity (i.e., 80 vs. 79 % ee). This data supports the earlier conclusions of Brown, namely that it is the *N*-H aldimine that is reacting with the AlIB(Ipc)₂ [4]. The new reagent **1** is evidently exhibiting similar behavior (Table 1).

Table 1 Asymmetric allylboration of the *N*-H imines derived from RCH = NTMS with **1**.

R in RCH=NH	4 (%)	Series	6 (%)	Abs. config.	$[\alpha]_{\text{D}}^{20}(\text{c}, \text{CHCl}_3)$	% ee ^a
Ph	50(-)	a	90(79) ^b	<i>R</i>	+39.8 (1.88)	80(79) ^b
2-ClC ₆ H ₄	60	b	70	<i>R</i>	+53.3 (1.73)	80
4-MeOC ₆ H ₄	66	c	70	<i>R</i>	+26.9 (1.33)	89
4-ClC ₆ H ₄	68	d	87	<i>S</i> ^c	-26.3 (1.39)	80
2-C ₄ H ₃ S	70	e	78	<i>R</i>	+20.7 (1.50)	86
3-C ₅ H ₄ N	60	f	60	<i>R</i>	+30.8 (1.52)	76
Bn ^b	–	g	60	<i>R</i>	-27.0 (1.3) ^d	68
<i>c</i> -Hx ^b	–	h	70	<i>R</i>	+6.0 (1.3) ^d	80

^aOptical purity determined through its Mosher amide using ¹³C and ¹H NMR.

^bThe *N*-DIBAL imine precursor was used.

^cThe (+)-**1S** reagent was employed.

^dThese values are $[\alpha]_{\text{D}}^{22}(\text{c}, \text{CH}_2\text{Cl}_2)$.

Employing *N*-TMS imine precursors, a nonoxidative work-up with PE was used to recover and recycle **4**. The conversion of **5** (¹¹B NMR δ 46–51) to **4** and **6** was slow, requiring 10 h at reflux temperature in MeCN. The acidic hydrolysis (2 M HCl (aq.)) of **5** was used for the isolation of **6** from the *N*-DIBAL imine reactions (**a**, **g**, **h**). The amines **6** were isolated in good yields (60–90 %) in 68–89 % ee. These selectivities obtained with **1** are generally comparable to those obtained with AlIB(Ipc)₂ from either the TMS or DIBAL imine precursors to the reacting *N*-H aldimines [4,12]. The new procedures use the air-stable crystalline complexes **4** as precursors to the allylboranes **1**. The reaction protocol for the TMS imines generates these complexes for the direct recycling of the chiral borane moiety. Since AlIB(Ipc)₂ employs air-sensitive precursors such as MeOB(Ipc)₂, which are difficult to handle and purify, using **1** for these allylations is operationally simple by comparison.

REACTIVITY OF **1** WITH *N*-SUBSTITUTED ALDIMINES

Interestingly, Chen and Brown had observed that *N*-TMS imines failed to react with either methanol or water at -78 °C in the absence of the organoborane [13]. However, rapid conversion to the *N*-H imines occurs in the presence of trialkylboranes such as EtB(Ipc)₂. They proposed the transition-state model **7** illustrated in Fig. 3 to explain this process.

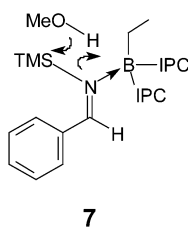


Fig. 3 Chen/Brown proposed transition-state model for the borane-mediated methanolysis of *N*-TMS aldimines.

It is somewhat surprising that the process is viewed in this way because there would appear to be a number of issues which would argue against such an interpretation. However, it has gained some acceptance [12]. This prompted us to address these issues with our systems. For one, the *N*-TMS aldimines show no tendency to complex trialkylboranes. Also, the *syn*-*N*-TMS imine needed to form the above complex is highly energetically disfavored (molecular mechanics (MM) calculations suggest ~14 kcal/mol higher than the *anti*-isomer). In fact, these same calculations suggest that formation of analogous *syn*-imine/**1** complex is highly endothermic (i.e., +23 kcal/mol) [14]. This means that very little of the *syn*-aldimine and even less of its borane complex would be available to react with MeOH. *The TS model shown in Fig. 3, therefore, must be viewed as essentially a highly organized termolecular process!* This seems unlikely to be responsible for this rapid low-temperature reaction. Moreover, while nucleophilic attack at silicon can follow a retention mechanism (e.g., $R_3SiOMe \rightarrow R_3SiH$ with $LiAlH_4$), these processes are sterically demanding and normally involve strong interactions between the nucleophilic species and a poor leaving group [15].

*Is there a more reasonable explanation for this hydrolysis process and the subsequent allylboration of the resulting *N*-H aldimines?* We had previously observed that **1** reacts smoothly with methanol at room temperature to form **3** (Fig. 4) [5]. This certainly suggested that the prior equilibrium complexation of MeOH with **1** could be occurring ultimately leading to the observed process. We chose to examine the effect of MeOH on the ^{11}B NMR spectrum of **1**, which exhibits an incremental upfield shift with each added amount of MeOH. By contrast, added *N*-TMS imines have no detectable effect on ^{11}B NMR spectrum of **1**. This behavior indicates that MeOH, rather than the *N*-TMS imine, is likely to complex **1** under the hydrolysis conditions (i.e., **8**). From MM calculations, the formation of **8** is far less endothermic (+4.5 kcal/mol) than is the formation of the *syn*-imine/**1** complex.

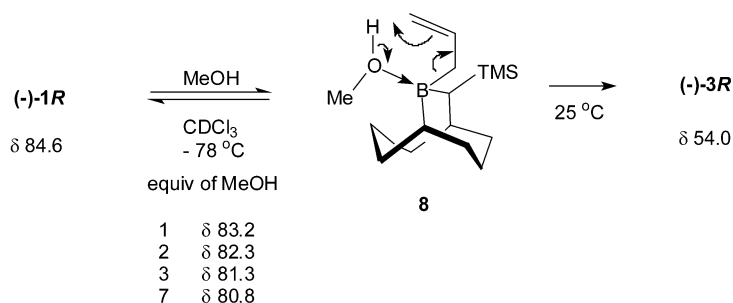


Fig. 4 Equilibrium complexation of MeOH with **1**.

Organoboranes are well known to increase the acidity of protic reagents such as MeOH. The ability of **8** to function as an acid is evident from its conversion to propene and **3**. Moreover, the protonation of the *anti*-*N*-TMS imine with **8** provides a convenient way to generate a source of nucleophilic methoxide (**10**) as well as electrophilic silicon (**9**) in a single process. The reaction of **9** with **10** is well

precedented. Their reaction produces the observed TMSOMe and the *syn*-*N*-H imine **11**. Our calculations indicate that this process is exothermic overall from **8** and the *N*-TMS imine. However, with the correct geometry to complex **1**, **11** can now form **13**, which is the lowest energy adduct, in an exothermic process (-5 kcal/mol). This leads to the correct prediction for the observed stereochemistry for **6**. Compared to the allylation of aldehydes with **1**, which gives 96 \rightarrow 99 % ee, the somewhat lower ee's observed for **11** are consistent with the lesser difference between the effective size of NH vs. allyl compared to O vs. allyl. This leads to an increase in the amount of attack of the imine on the side of **1** opposite to the TMS group and lower ee. Thus, through the processes illustrated in Figs. 4 and 5, it is possible to proceed through the borane-mediated hydrolysis of the *N*-TMS imines without invoking unrealistically high-energy intermediates.

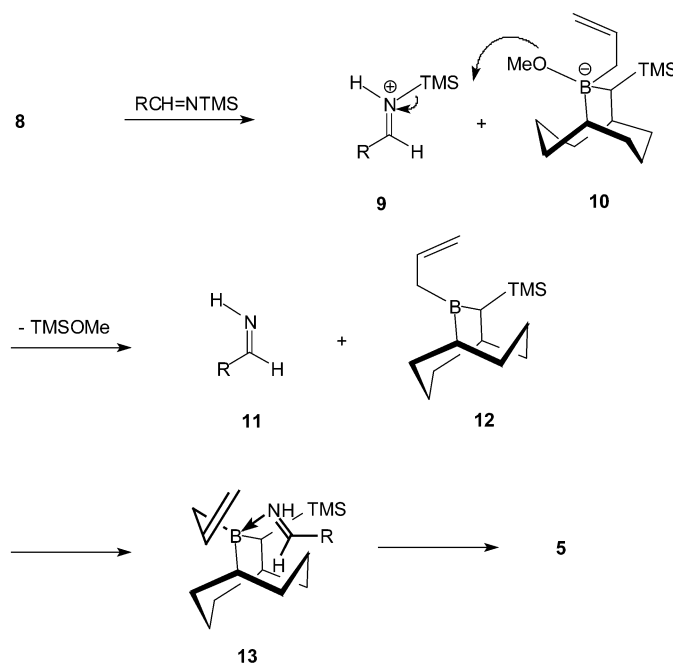


Fig. 5 Proposed mechanism for the hydrolysis of *N*-TMS imines and the allylation of *N*-H imines with **1**.

CONCLUSIONS

The new process of the asymmetric allylboration of *N*-H aldimines, generated from either *N*-TMS or *N*-DIBAL aldimines, with *B*-allyl-10-trimethylsilyl-9-borabicyclo[3.3.2]boranes **1** has been reported. The process is efficient (60–90 %) and highly enantioselective (68–89 % ee). The mechanistic aspects of the conversion of the *N*-TMS aldimines to their reactive *N*-H counterparts were examined both experimentally and computationally. These studies suggest that the model previously proposed for the related RB(Ipc)₂-mediated process was too high in energy. A more realistic model is proposed which involves the protonation of the imine by a MeOH/borane complex **8** followed by nucleophilic attack at silicon of the resulting immonium ion (**9**) by the methoxyborate species **10**. The origin of the observed product stereochemistry was also discussed in terms of the most stable pre-transition-state imine/borane complex **13**. These new reagents **1** are easily prepared and recycled from stable and user-friendly organoborane precursors. They exhibit similar selectivities to those observed with the AlB(Ipc)₂ reagents. These features make them highly attractive alternatives to existing reagents and processes for the asymmetric allylation of aldimines.

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