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Strict Reagent Control in the Asymmetric Allylboration of *N*-TIPS-α-Amino Aldehydes with the *B*-Allyl-10-TMS-9-borabicyclo[3.3.2]decanes‡

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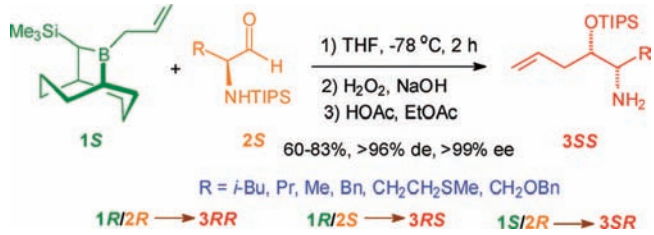
ABSTRACT



The allylboration of enantiomerically pure *N*-triisopropylsilyl-α-amino aldehydes (2) with *B*-allyl-10-trimethylsilyl-9-borabicyclo[3.3.2]decanes (1) proceeds cleanly at −78 °C, exhibiting essentially complete reagent control. After an oxidative workup, an HOAc-mediated *N*→*O* TIPS rearrangement facilitates the clean formation of stable *O*-TIPS protected *β*-amino alcohol derivatives 3 which are isolated in 60−83% yields in ≥96% de and >99% ee. For the leucinal series (R = *i*-Bu), an efficient entry to either statine (8a*SS*) or *epi*-statine (8a*RS*) is reported illustrating the versatility of this potent 1/2 combination.

Recently, we reported the simple preparation of the *B*-allyl-10-trimethylsilyl-9-borabicyclo[3.3.2]decanes (**1**) from the reaction of allylmagnesium bromide in ether with air-stable crystalline pseudoephedrine borinic ester complexes.[1] These robust reagents exhibit remarkable selectivities in their additions to aldehydes at −78 °C (96−99% ee). While only a very limited number of chiral aldehydes have been examined with **1**, a high level of reagent control has been observed in these examples.[1,2] The present study was designed to address the allylation of chiral α-amino aldehydes to provide a simple entry to functionalized *β*-amino alcohols which have a variety of useful applications.

The substrate-controlled allylation of *N*-protected-α-amino aldehydes with achiral reagents can involve either nonchelation or chelation-controlled additions which selectively produce *anti* (*erythro*) and *syn* (*threo*) diastereomeric products, respectively.[3] A more versatile strategy for the stereoselective synthesis of *β*-amino alcohols employs the addition of chiral reagents to chiral *N*-protected α-amino aldehydes. Allyltitanium complexes and especially organoboranes such as diisopinocampheylborane and tartrate-based boronic ester reagents have been used with variable levels of diastereoselectivity for these substrates.[4] This phenomenon can often be attributed to

‡ This work is dedicated to Professor Donald S. Matteson, an outstanding chemist and good friend, in the year of his 77th birthday.

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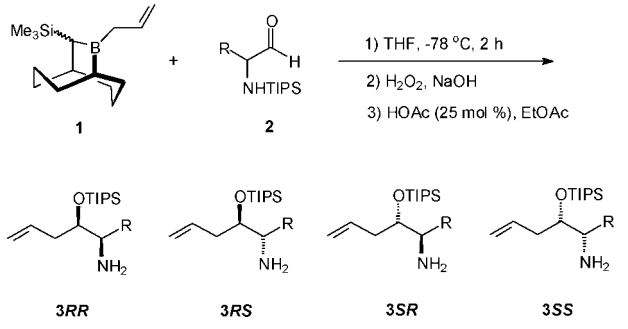
partially racemized amino aldehydes (e.g., Garner's *N*-Boc serine-based aldehyde).

To address these issues, we recently reported the synthesis of the chemically and configurationally stable *N*-triisopropylsilyl (TIPS) α-amino aldehydes (**2**) as enantiomerically pure compounds.[5] These new *N*-protected α-amino aldehydes were strategically designed to exhibit a complete absence of chelation control unlike many *N*-protected α-amino aldehydes. This behavior was expected to result from the well-known ability of the TIPS group to retard reactions at adjacent centers.[6] Moreover, in contrast to the doubly substituted *N*,*N*-dibenzyl derivatives, which can exert a strong stereochemical bias on the additions to the aldehydic moiety, use of a single bulky group (*e.g.*, *N*-9-phenylfluoren-9-yl) results in essentially stereorandom additions.[3c,7] *This is precisely what is needed for a strictly reagent-controlled process and* ***2*** *meets these requirements.* We also envisaged the *N*→*O* TIPS migration of the initially formed adducts **4** through a mild acid-catalyzed process to the more stable and versatile *O*-protected free amines **3**. Thus, we viewed the allylboration of **2** with **1** as a potentially ideal combination for the reagent-controlled allylation of α-amino aldehydes. Representative systems were chosen to establish the generality of the approach to the asymmetric synthesis of *O*-TIPS protected *β*-amino alcohols **3** (Scheme 1). These results are presented in Table 1.

Scheme 1



Initially, the allylations of alaninal (**2c*S***) and O-benzylserinal (**2f*S***) were examined with allylmagnesiun bromide in ether producing, after TIPS rearrangement, **3c** and **3f** in 56:44 and 52:48 *syn/anti* ratios, respectively. Essentially no substrate control is observed with **2** in this process. Thus, the remarkable selectivity of **1** in the allylboration reaction can completely dominate the process as is observed from the results illustrated in Table 1. In each case, the BBD reagents **1** add to **2** to provide essentially a single isomeric amino alcohol with the new stereogenic center being determined solely by the enantiomer of **1** chosen for the process. Thus, **1*S*** gives **3** with the (4*S*) configuration in ≥99% ee and **1*R*** produces **3** with the (4*R*) configuration with the same high level of selectivity. Any enantiomeric impurities in **2** are faithfully reflected as diastereomeric products, a phenomenon only observed for methional (**2e**) and *O*-benzylserinal (**2f**) (≤2%).[8]

Table 1. Asymmetric Allylboration of Representative Amino Aldehydes **2** with **1**

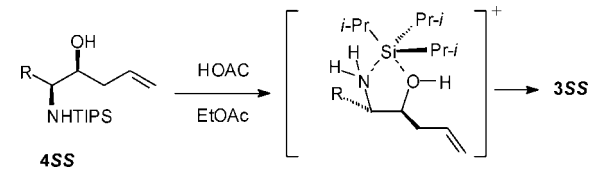
1	**2**	**3**, R	dr[a] *syn*/*anti*	ee[b]	yield (%)[c]	abs. config.[d,e]
S	*S*	**a**, *i*-Bu	<99:1	99	83	4*S*,5*S*
S	*R*	**a**, *i*-Bu	<1:99	99	73	4*S*,5*R*
R	*R*	**a**, *i*-Bu	<99:1	99	83	4*R*,5*R*
R	*S*	**a**, *i*-Bu	<1:99	99	66	4*R*,5*S*
S	*S*	**b**, Pr	99:1	99	71	4*S*,5*S*
S	*R*	**b**, Pr	1:99	99	62	4*S*,5*R*
R	*R*	**b**, Pr	99:1	99	70	4*R*,5*R*
R	*S*	**b**, Pr	1:99	99	64	4*R*,5*S*
S	*S*	**c**, Me	<99:1	99	70	4*S*,5*S*
R	*S*	**c**, Me	<1:99	99	60	4*R*,5*S*
S	*S*	**d**, Bn	<99:1	99	68	4*S*,5*S*
R	*S*	**d**, Bn	<1:99	99	60	4*R*,5*S*
S	*S*	**e**, $(CH_2)_2SMe$	98:2	99	80	4*S*,5*S*
R	*S*	**e**, $(CH_2)_2SMe$	2:98	99	60	4*R*,5*S*
S	*S*	**f**, CH_2OBn	98:2	99	76	4*S*,5*S*
R	*S*	**f**, CH_2OBn	2:98	99	70	4*R*,5*S*

[a] Determined by ^{13}C NMR of the crude before TIPS N→O migration. [b] Calculated by examination of the Mosher's amide derivatives of **3**. [c] Yields of pure and isolated materials. [d] Absolute configuration of the isomers of **3a** were determined by 1-D and 2-D NMR examination of pyrrolidinones **7a*SS*** and **7a*RS*** and confirmed by the synthesis of statine **8a*SS*** and *epi*-statine **8a*RS***. [e] Absolute configuration of **3b-f** were determined by NMR

Previously, we had employed both oxidative (H_2O_2, base) and nonoxidative (pseudoephedrine) workup procedures for the allylboration of aldehydes with **1**.[1] However, since both pseudoephedrine and **3** are *β*-amino alcohol derivatives, we chose to employ an oxidative workup procedure to avoid potential separation and isolation problems.

In the case of leucinal **2a**, the initially formed *N*-TIPS product **4a** (R = *i*-Bu) proved to be unstable with respect to chromatography or distillation. Based upon the apparent sensitivity of these systems to an acid medium, we developed an efficient protocol to effect the smooth *N*→*O* TIPS migration with dry HOAc (25% mol) in EtOAc (Scheme 2). As expected, the transposition is faster for the *threo*

Scheme 2



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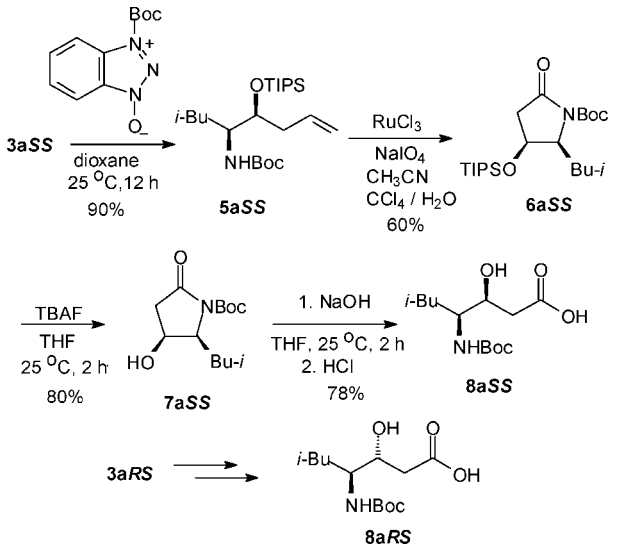
(8) No diastereomeric amplification is observed in any step of the process as revealed from the 1:1 reaction of **1*R*** with (±)-**2a** which gives the borinate adducts, **4**, crude **3**, pure **3**, and their Mosher amides, all in a 1:1 diastereomeric ratio (see Supporting Information).

isomers (e.g., **4a*SS***) than for their *erythro* (e.g., **4a*SR***) counterparts. Hence, in general, a reaction time of 72 h at 25 °C was employed for this isomerization to ensure its completion in all cases. After neutralization with TEA, the *β*-amino alcohol derivatives **3** are completely stable to standard silica gel chromatography and can be isolated as analytically pure compounds in 60−83% yields. NMR analysis of the well resolved signals from the corresponding Mosher amides revealed a consistently high level of enantiomeric purity in **3** (major isomer ≥99% ee in every case). The existence of the free 1°-amine in **3a** was observed in the FTIR spectrum by the presence of the N−H asymmetric stretch at 3389 cm^{-1} and the N−H symmetric stretch at 3321 cm^{-1} as well as by the absence of the O−H stretch. This process selectively transfers the protection from *N*→*O* thereby further utilizing the TIPS group protection for subsequent conversions.

We chose to prepare the known *N*-Boc derivatives of statine (**8a*SS***) and *epi*-statine (**8a*RS***) to demonstrate the versatility of the present method and to confirm the absolute stereochemistry of **3** (Scheme 3). The leucine-based compounds have been studied extensively. Statine has been found in the backbone of pepstatin, a microbial inhibitor of aspartic proteolytic enzymes such as pepsin, cathepsin D and rennin.[9]

Scheme 3



Moreover, *epi*-statine is of interest because it is a member of the anti series of statine analogues present in depsipeptides with biological activitiy.[10]

Preparation of the Boc carbamates **5a*SS*** and **5a*RS*** initially proved difficult, a problem overcome with 1-*N*-(*tert*-butoxycarbonyl)-1*H*-benzotriazol-3-*N*-oxide[11] in dioxane which provides **5** in excellent yields as mixtures of *E*/*Z* rotamers (Scheme 3). Catalytic oxidation[12] of these **5a** isomers with RuO_4 through the Sharpless protocol produces the corresponding *cis*- or *trans*-4-*O*-TIPS-5-isobutylpyrrolidinones as single isomers (**6a*SS*** and **6a*RS***). Treatment of **6a** with 1.1 equiv of TBAF in THF at room temperature for 2 h afforded the corresponding desilylated pyrrolidinones **7a** in good yields. For these, 2D-NMR experiments were conducted (COSY 45, HMQC and NOESY) to establish the *cis* relationship of the groups on C-4 and C-5. All these data are in agreement with reported values as is the optical rotation.[13] NOESY experiments also revealed no cross-peaks between H-4 and H-5 in **7a*RS***.

The hydrolysis of the appropriate lactams **7** in THF under basic conditions furnished the known *N*-Boc-statine **8a*SS***

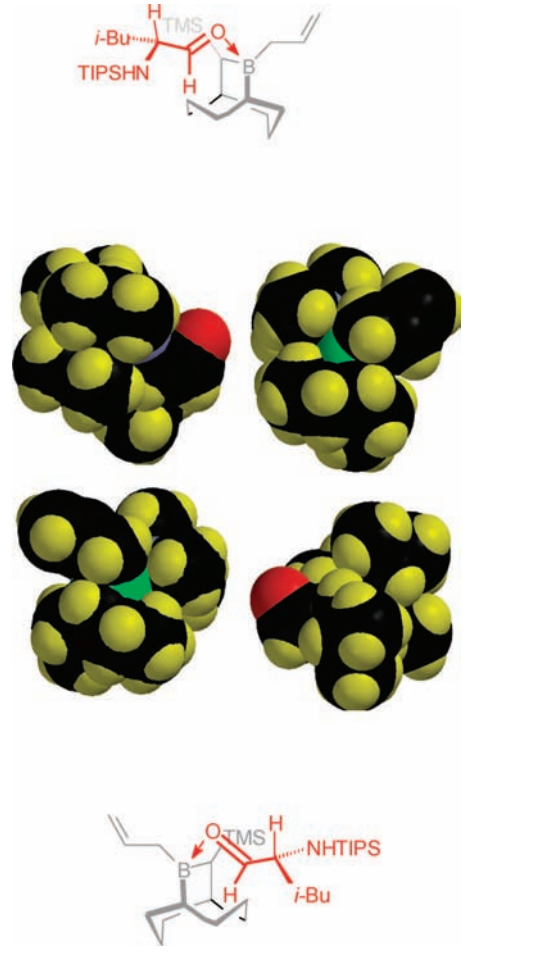


Figure 1. Space-filling MM Models of **2a*S*** paired with **1*S*** and **1*R***. Energy-minimized pretransition state complexes which represent a model for the observed selectivities (color code for atoms: C, black, H, yellow, O, red; B, green, N, purple, Si, gray).

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(15) Calculations were conducted using Spartan 06 programs.

and *epi-N*-Boc-statine **8a*RS*** in good yields. These compounds were obtained as mixtures of amide rotamers. The optical rotations, in addition to the ^{1}H- and the ^{13}C NMR spectra of the major rotamers in $CDCl_3$ are in full agreement with the reported data.[14]

In the above study, we have demonstrated that the **1/2** combination represents a powerful new approach to stereochemically pure 1,2-amino alcohols **3**. Strict reagent control is observed because, not only is **1** an incredibly selective reagent, but also, the *N*-TIPS substitution essentially removes any stereochemical bias associated with amino aldehyde substrates in these additions. We were interested in identifying possible features of these compounds that could explain this reactivity. Toward this end, we examined simple MM-generated models for these reagent/substrate combinations.[15] It was found that the formyl groups in **2** dramatically protrude from the molecule's remaining bulk, permitting *O*-coordination and nucleophilic addition to the carbonyl from either face (Figure 1). The well defined chiral pockets in **1** highly favor attack of the aldehyde *cis* to the 10-TMS to provide less severe steric repulsions for the O/TMS vs allyl/TMS interactions. Thus, the fact that **2** is accessible from either diastereotopic face leads to reagent control with allylborations employing the highly selective *B*-allyl-10-TMS-9-BBDs **1**.

As previously noted, both pinene- and tartrate-derived allylboranes have been used for the asymmetric allylation of *N*-protected α-amino aldehydes.[4] The new chemistry described herein provides major advances in this process. By utilizing configurationally stable *N*-TIPS α-amino aldehydes **2** with near perfect optical purities, obtaining diastereomeric products from enantiomeric impurities in the amino aldehydes employed is no longer problematic.[4b,c] With **2**, substrate control is also eliminated in this process. Thus, with the remarkable level of reagent control exhibited by **1**, match/mismatch considerations are moot and lowered selectivities and even unexpected products are avoided in traditionally mismatched cases.[2,16] Completely predictable stereochemistry can be incorporated into **3** through the appropriate choice of a **1/2** combination. This chemistry reflects the powerful utility of silicon in the orchestration of organoborane conversions.[1,6,17]

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Supporting Information Available: Full experimental procedures, characterization data, selected spectra for **3**, **5**−**8**, and derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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