Asymmetric Synthesis of Allylsilanes by the Borylation of Lithiated Carbamates: Formal Total Synthesis of (−)-Decarestrictine D**

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Chiral allylsilanes are highly valuable nucleophiles in stereoselective organic synthesis because of the multitude of asymmetric transformations that they can undergo. For example, β-hydroxy allylsilanes have been used extensively by the groups of both Panek and Roush in natural product synthesis. Amongst the most useful applications in recent years are the [3+2] annulation and the [4+2] annulation as they allow facile access to furans and pyrans. However, the synthesis of substituted β-hydroxy allylsilanes is not always straightforward and usually requires multiple steps. The broad synthetic utility of β-hydroxy allylsilanes motivated us to develop more efficient synthetic routes to such intermediates.

We recently reported a new method for the homologation of boronic esters and boranes by employing the lithiated carbamates reported by Hoppe et al. Our method involved the use of carbamates derived from primary and secondary alcohols, which led to the formation of secondary and tertiary alcohols in high enantiomeric ratios after oxidation. The reaction could be extended to a one-pot, multiple homologation process and its application in the synthesis of (±)-faranal was demonstrated. In extending this methodology further, we considered its application in the stereocontrolled, one-pot synthesis of β-hydroxy allylsilanes. We envisioned that the reaction of a lithiated carbamate with β-silyl vinyl borane would form the intermediate allylborane which could react with an aldehyde to give an Z-configured anti-allylsilane (Scheme 1). Subsequent epoxidation and elimination/ring-opening could then provide a stereocontrolled route to 2-ene-anti-1,4-diols, a common motif in natural products (Scheme 1). Herein we detail our success in developing this methodology and its application in synthesis.

Our initial studies, however, revealed some unexpected results (Scheme 2). For example, the reactions of lithiated carbamates with B-Ph-9-BBN and subsequent oxidation gave the corresponding alcohols in 97:3 e.r. and with complete retention of configuration. Surprisingly, reaction of the lithiated carbamate with borane and subsequent trapping with benzaldehyde gave allylsilane in only 71:29 e.r. More alarmingly, lithiated carbamate gave allylsilane in 93:7 e.r. but now with inversion of the expected stereochemistry. Through a careful set of control experiments we established that the recalcitrant step causing the unexpected selectivity was the reaction of the lithiated carbamate with the borane, and that the reaction was critically dependent upon the nature of the amine that was complexed to the lithiated carbamate.

In our detailed studies we used the related stannane since the stereochemistry associated with the synthesis of its subsequent lithiation, and electrophilic trapping had been reported and rigorously proven by Hoppe et al. We first explored diamine-free reactions by initial formation of the lithiated carbamate with borane and subsequent trapping with benzaldehyde gave allylsilane in only 71:29 e.r. More alarmingly, lithiated carbamate gave allylsilane in 93:7 e.r. but now with inversion of the expected stereochemistry. Through a careful set of control experiments we established that the recalcitrant step causing the unexpected selectivity was the reaction of the lithiated carbamate with the borane, and that the reaction was critically dependent upon the nature of the amine that was complexed to the lithiated carbamate.
stannane 12 and subsequent tin–lithium exchange.[14] After the addition of borane 3 and benzaldehyde, allylsilane 7a was formed in 94:6 e.r., but now with essentially complete retention of configuration (Table 1, entry 1). Addition of sterically undemanding diamines to the lithiated carbamate led to the same major enantiomer (Table 1, entries 2 and 3), whereas addition of the hindered diamine (−)-sparteine led to almost complete inversion of the configuration (Table 1, entry 4). The stereochemistry of the diamine did not influence the stereochemical outcome of the reaction since the (+)-sparteine surrogate, reported by O’Brien and co-workers,[15] also led to inversion of configuration, albeit with lower selectivity (Table 1, entry 5). Similar inversion was obtained with the achiral, hindered diamine bispi[16] (Table 1, entry 6). From these results it was clear that the main factors influencing the stereochemical outcome of the reaction were the bulk [(−)-sparteine is more hindered than (+)-sparteine surrogate] and rigidity of the diamine and not its stereochemistry.

The discovery that in the case where R is methyl (which constitutes the most important example), the diamine-free lithiated carbamate leads predominantly to retention of configuration and the (−)-sparteine complexed to the lithiated carbamate leads to predominantly inversion of stereochemistry, is especially useful since it obviates the need to use the (+)-sparteine surrogate ligand.[17] Furthermore, the process was general for a range of aldehydes, thereby providing a simple method for accessing both sets of enantiomeric β-hydroxy allylsilanes (Table 2, entries 1–6).

Table 1: Detailed studies of the lithiation/borylation reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Stereochemical outcome</th>
<th>7a/ent-7a Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>retention</td>
<td>94:6 95</td>
</tr>
<tr>
<td>2</td>
<td>TMEDA[2]</td>
<td>retention</td>
<td>91:9 78</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>retention</td>
<td>92:8 87</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>inversion</td>
<td>8:92 83</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>inversion</td>
<td>35:65 50</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>inversion</td>
<td>35:65 94</td>
</tr>
</tbody>
</table>

[a] TMEDA = N,N,N',N'-tetramethylethylenediamine.

Table 2: Stereocontrolled one-pot synthesis of β-hydroxy allylsilanes.[3]

<table>
<thead>
<tr>
<th>Method A:</th>
<th>1) nBuLi (−)-sparteine</th>
<th>2) borane 3</th>
<th>4) H2O2, NaOH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>entry-4</td>
<td>ent-7[a]</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: lithiated carbamate (1.0 equiv), borane 3 (1.3 equiv), aldehyde (2.0 equiv), and workup with H2O2/NaOH.
[b] Method A was used. [c] Method B was used. [d] Yield of isolated product (see the Supporting Information). [e] The e.r. value was determined by GC or HPLC methods using a chiral stationary phase.
[f] Major enantiomer originates from inversion of the configuration during the reaction of lithiated carbamate with borane 3. [g] Major enantiomer originates from retention of the configuration in the reaction of lithiated carbamate with borane 3. [h] Ratio was determined by 1H NMR spectroscopy.

The new, diamine-free protocol also solved the problem of low enantioselectivity observed with lithiated carbamate 2b. Thus, employing stannane 13[13] (Method B) led to β-hydroxy allylsilanes with high e.r. values (Table 2, entries 7–9). These reactions proceed via transition state 6 in which the R group occupies an axial position to avoid steric repulsion from the bulky 9-BBN moiety.

The stereochemical outcome of the reactions of the lithiated carbamates with boranes can be rationalized by considering the steric environment around the lithiated carbamate (Figure 1). In general, there is an inherent preference for nonmesomeric stabilized lithiated carbamates (with or without (−)-sparteine complexed) to react with boranes, and indeed all other electrophilic reagents (e.g., SiMe3Cl, CO2, Me3SnCl, MeI[3], or boronic esters[3,5]) with stereoretention.[7] Evidently, reactions with alkenyl boranes are more finely balanced. In the absence of bulky diamines the lithiated carbamates react with retention of configuration as expected (Figure 1, A and C). However, the unhindered C–Me lithiated carbamate possessing a bulky diamine reacts with the borane with inversion since the face bearing the
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Table 3: Synthesis of 2-ene-1,4-diols 9 by the epoxidation/olefination of \( \beta \)-hydroxy allylsilanes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R )</th>
<th>( R' )</th>
<th>Yield [%]</th>
<th>( E/Z )</th>
<th>anti/syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_3)</td>
<td>nBu</td>
<td>96</td>
<td>&gt;25:1</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)</td>
<td>Cy</td>
<td>89</td>
<td>&gt;25:1</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>3</td>
<td>CH(_3)</td>
<td>Ph</td>
<td>93</td>
<td>&gt;25:1</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>4</td>
<td>PhCH(_2)CH(_3)</td>
<td>nBu</td>
<td>90</td>
<td>&gt;25:1</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>5</td>
<td>PhCH(_2)CH(_3)</td>
<td>Cy</td>
<td>82</td>
<td>&gt;25:1</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>6</td>
<td>PhCH(_2)CH(_3)</td>
<td>Ph</td>
<td>88</td>
<td>&gt;25:1</td>
<td>&gt;25:1</td>
</tr>
</tbody>
</table>

[a] Yield of isolated product (2 steps). [b] Ratio was determined by \(^1\)H NMR spectroscopy.

Figure 1. Rationale for the stereochemical outcome considering the steric environment.

lithium (retentive pathway) is blocked by the amine (Figure 1, B). As the substituent on the carbamate becomes larger, both faces become rather hindered and as such, reactions occur with both retention and inversion leading to low enantioselectivity (Figure 1, D).

It should be noted that the electrophilic substitution of benzyl \([8]\) and alkenyl carbamates \([18b]\) is less predictable and depends upon the substituents of the carbanion, the electrophile, and the ligands complexing the lithium cation. \([18c]\)

The silyl group is a powerful stereocontrolling element in synthesis. This was demonstrated by epoxidation of allylsilanes \(7\) using \( m \)CPBA \([19]\) and subsequent acid-catalyzed elimination \([20]\) which gave the 2-ene-1,4-anti-diols \(9\) in high yields and with excellent diastereoselectivity in all cases (Table 3).

1,4-syn-Diols can also be prepared using this methodology simply by using an alternative boron reagent (Scheme 3).

Thus, reaction of lithiated carbamate \(2a\) with boronic ester \(14\) in the presence of MgBr\(_2\) and then addition of benzaldehyde gave the \( E \)-configured anti-\( \beta \)-hydroxy allylsilanes \(17\) in 20:1 d.r. and 98:2 e.r. In contrast to reactions with \( B \) lithiation \([18c]\), carbanion, the electrophile, and the ligands complexing the lithium cation \([18c]\).

Finally, the potential of this methodology is illustrated in the synthesis of \((\sim)\)-decarestrictine \(D\) \((28)\), a 10-membered lactone that has been isolated from \( Penicillium corylophilum\) and \( Polyporus tuberaster\). \([22]\) It displays selective and strong inhibition of liver cell cholesterol biosynthesis (HEP cells, \( I_C_{50} = 100 \, \text{nm} \)). From a structural point of view the four stereogenic centers, the unsaturated segment, and the 10-membered macrolactone pose significant synthetic challenges (Scheme 4). \([23]\) A retrosynthetic analysis of \(28\) led to seco acid

\[ \begin{align*}
\text{Scheme 3.} \quad & \begin{align*}
\text{Synthesis of syn-diol} \ 18 \ 	ext{through} \ (\sim)\-\beta\)-hydroxy allylsilanes \ 17: \\
& \begin{align*}
& \text{a) } \text{BuLi,} \ (-)\-\text{sparteine, } \text{Et}_2\text{O,} \ -78^\circ \text{C}, \ 5 \ h; \\
& \text{b) boronic ester} \ 14, \ -78^\circ -23^\circ \text{C}, \ 1 \ h; \\
& \text{c) MgBr}_2, \ 23^\circ \text{C}, \ 1 \ h; \\
& \text{d) } \text{PhCHO,} \ -25^\circ \text{C,} \ 18 \ h; \\
& \text{e) } \text{H}_2\text{O}_2/\text{NaOH}; \ 62 \% \text{ yield (e-a, one pot; e.r. } \approx 98:2, \, E/Z = 20:1); \\
& \text{f) } m\text{CPBA,} \ \text{NaHCO}_3, \ \text{CH}_2\text{Cl}_2; \\
& \text{g) } \text{AcOH,} \ \text{MeOH,} \ 85 \%, \ (E\text{-configured syn:} \\
& Z\text{-configured syn)}; \\
& E\text{-configured anti } \approx 15:4:1. \ m\text{CPBA} = \text{meta-chloroperbenzoic acid.}
\end{align*}
\end{align*}
\end{align*} \]

\[ \begin{align*}
\text{Scheme 4.} \quad & \begin{align*}
\text{Synthesis of seco acid} \ 27: \\
& \begin{align*}
& \text{a) SEMCl,} \ \text{DIEA,} \ \text{CH}_2\text{Cl}_2, \ 93 \%; \\
& \text{b) } \text{LiAIH}_3, \ \text{THF,} \ 95 \%; \\
& \text{c) } \text{CIC(O)N/Pr}_2, \ \text{Et}_2\text{N,} \ \text{CH}_2\text{Cl}_2, \ 57 \% \ (95 \% \text{ brsm);} \\
& \text{d) } (\sim)\-\text{sparteine surrogate, } \text{BuLi,} \ \text{Et}_2\text{O then } \text{Bu}_2\text{SnCl}, \ 72 \%, \ d.r. > 97:3; \\
& \text{e) } \text{BuLi,} \ \text{Et}_2\text{O,} \ \text{then borane 3,} \ \text{then aldehyde} 22, \ 85 \%, \ (Z/E > 25:1, \\
& \text{anti/syn } > 25:1); \\
& \text{f) } \text{mCPBA,} \ \text{NaHCO}_3, \ \text{CH}_2\text{Cl}_2, \ \text{then aqueous} \\
& \text{Na}_2\text{SO}_4; \ 2; \ \text{AcOH,} \ \text{MeOH,} \ 78 \% \ \text{(two steps),} \ E/Z > 25:1, \ \text{anti/syn } > 25:1; \\
& \text{g) } \ \text{Dudley reagent (25),} \ \text{MgO,} \ \text{PhCF}_2, \ 57 \%; \\
& \text{h) } \text{LiOH,} \ \text{MeOH/THF/H}_2\text{O (2:2:1),} \ 90 \%; \\
& \text{i) } \text{TFA,} \ \text{CH}_2\text{Cl}_2, \ 77 \%. \ 8 \text{ nbenzyl,} \ \text{brms = based on recovered starting material,} \\
& \text{DIEPA = disopropylethylamine,} \ \text{Dudley reagent = 2-benzoxyl-1-methylpyridinium triflate,} \\
& \text{SEM = 2-(trimethylsilyl)ethoxymethyl,} \ \text{TFA = trifluoroacetic acid.}
\end{align*}
\end{align*}
\]
27 as a suitable target for a formal synthesis since it had been converted into the natural product in two steps by a Yamaguchi macrocyclization and subsequent debenzylation.\(^{[24]}\) The synthesis commenced with commercially available \(\beta\)-hydroxy ester 19 (Scheme 4). After protection using SEMCl, reduction, and carbamoylation, compound 20 was deprotonated with \(\text{BuLi}((+)-\text{sparteine-surrogate})\) and trapped with \(\text{BuSnCl}\) to yield stannane 21.\(^{[25]}\) The key step was the three-component coupling involving lithiation of 21 and then sequential addition of vinyl borane 3 and aldehyde 22.\(^{[26]}\) which gave the desired allylsilane 23 in 85% yield and essentially perfect stereoselectivity. Epoxidation and olefination led to diol 24, which was doubly benzylated using the Dudley reagent (25).\(^{[27]}\) This diol was found to be especially sensitive since alternative reagents led to complete decomposition. Saponification and removal of the SEM group gave sec acid 27 which completed the formal total synthesis.\(^{[24]}\)

In conclusion we have developed a novel, high-yielding, one-pot procedure for the stereocontrolled synthesis of allylsilanes with almost complete selectivity over the three elements of stereogenicity. In particular, it has been discovered that sparteine-complexed lithiated carbamates react with \(\beta\)-silylvinylboranes with inversion of configuration whereas the diamine-free lithiated carbamates react with retention of configuration. Epoxidation of the allylsilanes and subsequent acid-catalyzed elimination/ring-opening gave 2-ene-1,4-homologation with excellent yields and diastereoselectivity. Related \(\text{syn}\) diols could also be obtained albeit with lower levels of stereoselectivity. We have demonstrated the application of this methodology in a concise formal total synthesis of (\(-\))-decaerestrictine D. Additional applications of this efficient and highly stereoselective methodology in natural product synthesis are underway.

Received: March 1, 2010
Revised: March 25, 2010
Published online: May 5, 2010

**Keywords:** boranes - borates - homologation - lithium - natural products

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17) There are a few examples where (−)-sparteine can be used to generate either enantiomer of a product, for example: Y. S. Park, M. L. Boys, P. Beak, *J. Am. Chem. Soc.* 1996, 118, 3757–3758.

18) a) Reaction of less hindered vinyl boranes (e.g. trans-H,CH=CH-B-9BBN) show intermediate reactivity with the same carbamates: 2b reacts with complete retention of configuration but 2a reacts to give a mixture of products derived from retention and inversion of configuration. Carbamate 12 (dia-
with retention of configuration. This is probably because the lithium can complex with the oxygen atom of the boronic ester so that the boronic ester is delivered from the same face as the metal; see Ref. [8].


[25] Use of $s$BuLi/TMEDA and then Bu$_3$SnCl gave a 1:1 ratio of diastereomeric stannanes showing that the O–SEM group does not influence the lithiation step.
