

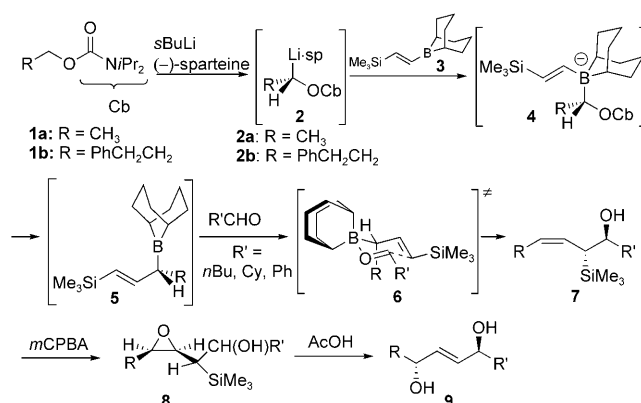
Asymmetric Synthesis of Allylsilanes by the Borylation of Lithiated Carbamates: Formal Total Synthesis of (–)-Decarestrictine D**

Michael Binanzer, Guang Yu Fang, and Varinder K. Aggarwal*

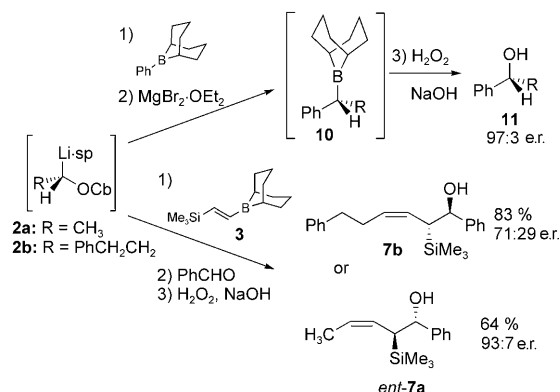
Chiral allylsilanes are highly valuable nucleophiles in stereo-selective organic synthesis because of the multitude of asymmetric transformations that they can undergo.^[1] For example, β -hydroxy allylsilanes have been used extensively by the groups of both Panek and Roush in natural product synthesis. Amongst the most useful applications in recent years are the [3+2] annulation^[2] and the [4+2] annulation^[3] as they allow facile access to furans and pyrans.^[4] However, the synthesis of substituted β -hydroxy allylsilanes is not always straightforward and usually requires multiple steps.^[5] 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^[6] by employing the lithiated carbamates reported by Hoppe et al.^[7] Our method involved the use of carbamates derived from primary and secondary alcohols, which led to the formation of secondary and tertiary^[8] 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.^[9] 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 **3**^[10] would form the intermediate allylborane **5**^[11] which could react with an aldehyde to give an *Z*-configured *anti*-allylsilane **7** (Scheme 1).^[12] Subsequent epoxidation and elimination/ring-opening could then provide a stereocontrolled route to 2-ene-*anti*-1,4-diols **9**, 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 **2a,b** with *B*-Ph-9-BBN and subsequent oxidation gave the corresponding alcohols **11a,b** in 97:3 e.r. and with complete retention of configuration.^[6] Surprisingly, reaction



Scheme 1. Proposed synthesis of β -hydroxy allylsilanes **7** and *anti*-diols **9**; Cb = *N,N*-diisopropylcarbamoyl, sp = (–)-sparteine, Cy = cyclohexyl.



Scheme 2. Initial studies of the one-pot reaction.

of the lithiated carbamate **2b** with borane **3** and subsequent trapping with benzaldehyde gave allylsilane **7b** in only 71:29 e.r. More alarmingly, lithiated carbamate **2a** gave allylsilane *ent*-**7a** 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 **12** since the stereochemistry associated with the synthesis of **12**, its subsequent lithiation, and electrophilic trapping had been reported and rigorously proven by Hoppe et al.^[13] We first explored diamine-free reactions by initial formation of

[*] Dipl.-Chem. M. Binanzer, Dr. G. Y. Fang, Prof. Dr. V. K. Aggarwal
School of Chemistry, University of Bristol
Cantock's Close, Bristol, BS8 1TS (UK)
Fax: (+44) 117-929-8611
E-mail: v.aggarwal@bristol.ac.uk
Homepage: <http://www.chm.bris.ac.uk/org/aggarwal/aggarhp.html>

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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

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

Entry	Additive	Stereochemical outcome	7a / ent-7a	Yield [%]
1	none	retention	94:6	95
2	TMEDA ^[a]	retention	91:9	78
3		retention	92:8	87
4		inversion	8:92	83
5		inversion	35:65	50
6	<i>i</i> Pr–N– N– <i>i</i> Pr	inversion	35:65	94

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

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 of configuration was obtained with the achiral, hindered diamine bispidine^[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 lithi-

ated 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 2: Stereocontrolled one-pot synthesis of β-hydroxy allylsilanes.^[a]

Method A:

$$R-CH_2-OCb \xrightarrow[2) \text{ borane } 3]{1) \text{ sBuLi } (-)\text{-sparteine}} \text{ent-4} \xrightarrow[4) \text{ H}_2\text{O}_2, \text{ NaOH}]{3) \text{ R'CHO}} R-CH=CH-CH(OH)-SiMe_3$$

Method B:

$$R-CH_2-OCb \xrightarrow[2) \text{ borane } 3]{1) \text{ nBuLi}} 4 \xrightarrow[4) \text{ H}_2\text{O}_2, \text{ NaOH}]{3) \text{ R'CHO}} R-CH=CH-CH(OH)-SiMe_3$$

12: R = CH₃ **13:** R = PhCH₂CH₂

Entry	R (substrate)	R'	Yield [%] ^[d]	7 / ent-7 ^[e]	Z/E ^[h]	anti/syn ^[h]
1	CH ₃ ^[b] (1a)	<i>n</i> Bu	67	7:93 ^[f]	> 25:1	> 25:1
2	CH ₃ ^[b] (1a)	Cy	65	7:93 ^[f]	> 25:1	> 25:1
3	CH ₃ ^[b] (1a)	Ph	64	7:93 ^[f]	> 25:1	> 25:1
4	CH ₃ ^[c] (12)	<i>n</i> Bu	95	95:5 ^[g]	> 25:1	> 25:1
5	CH ₃ ^[c] (12)	Cy	96	95:5 ^[g]	> 25:1	> 25:1
6	CH ₃ ^[c] (12)	Ph	95	94:6 ^[g]	> 25:1	> 25:1
7	PhCH ₂ CH ₂ ^[c] (13)	<i>n</i> Bu	81	98:2 ^[g]	> 25:1	> 25:1
8	PhCH ₂ CH ₂ ^[c] (13)	Cy	74	98:2 ^[g]	> 25:1	> 25:1
9	PhCH ₂ CH ₂ ^[c] (13)	Ph	81	98:2 ^[g]	> 25:1	> 25:1

[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**^[15] (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,^[13] or boronic esters^[8,9]) with stereoretention.^[17a] 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

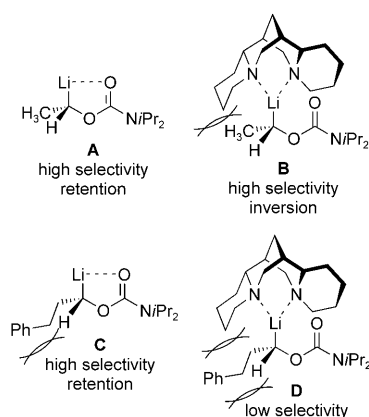
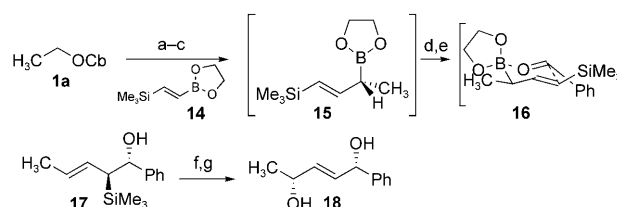


Figure 1. Rationale for the stereochemical outcome considering the steric environment.

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**).^[18a] 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 MgBr₂ and then addition of benzaldehyde gave the *E*-configured *anti*-β-hydroxy allylsilanes **17** in 20:1 d.r. and 98:2 e.r. In contrast to reactions with *B*-alkenyl-9-BBN derivatives, the reaction of the lithiated carbamate with boronic ester **14** occurred with retention of configuration, even in the presence of the bulky diamine.^[21] The reaction proceeds via transition structure **16** in which the small ester



Scheme 3. Synthesis of *syn*-diol **18** through (*E*)-β-hydroxy allylsilanes **17**: a) *s*BuLi, (–)-sparteine, Et₂O, –78 °C, 5 h; b) boronic ester **14**, –78 °C → 23 °C, 1 h; c) MgBr₂, 23 °C, 1 h; d) PhCHO, –25 °C, 18 h; e) H₂O₂/NaOH; 62% yield (a–e, one pot; e.r. = 98:2, *E/Z* = 20:1); f) *m*CPBA, NaHCO₃, CH₂Cl₂; g) AcOH, MeOH, 85%, *E*-configured *syn*: *Z*-configured *syn*: *E*-configured *anti* ≈ 15:4:1. *m*CPBA = *meta*-chloro-perbenzoic acid.

ligand on boron allows the methyl group to occupy the less hindered equatorial position, thereby resulting in the formation of the *E* double bond. Subsequent epoxidation/olefination gave *syn*-diol **18**. The moderate diastereoselectivity was expected since the conformation of *E* allylsilanes is less well-controlled than their *Z* counterparts, leading to lower diastereoselectivity in the epoxidation step.^[19]

Finally the potential of this methodology is illustrated in the synthesis of (–)-decastrictine 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, IC₅₀ = 100 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

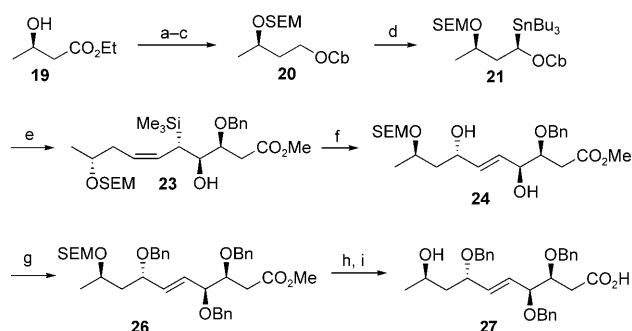
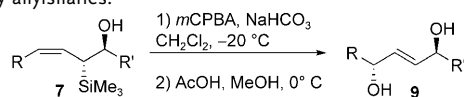
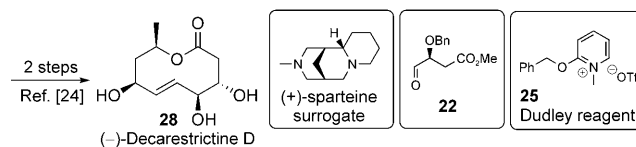


Table 3: Synthesis of 2-ene-1,4-diols **9** by the epoxidation/olefination of β-hydroxy allylsilanes.



Entry	R	R'	Yield [%] ^[a]	<i>E/Z</i> ^[b]	<i>anti/syn</i> ^[b]
1	CH ₃	<i>n</i> Bu	96	> 25:1	> 25:1
2	CH ₃	Cy	89	> 25:1	> 25:1
3	CH ₃	Ph	93	> 25:1	> 25:1
4	PhCH ₂ CH ₂	<i>n</i> Bu	90	> 25:1	> 25:1
5	PhCH ₂ CH ₂	Cy	82	> 25:1	> 25:1
6	PhCH ₂ CH ₂	Ph	88	> 25:1	> 25:1

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



Scheme 4. Synthesis of seco acid **27**: a) SEMCl, DIPEA, CH₂Cl₂, 93%; b) LiAlH₄, THF, 95%; c) ClC(O)NiPr₂, Et₃N, CH₂Cl₂, 57% (95% brsm); d) (+)-sparteine surrogate, *s*BuLi, Et₂O then Bu₃SnCl, 72%, d.r. > 97:3; e) *n*BuLi, Et₂O, then borane **3**, then aldehyde **22**, 85%, (*Z/E* > 25:1, *anti/syn* > 25:1); f) 1. *m*CPBA, NaHCO₃, CH₂Cl₂ then aqueous Na₂S₂O₃; 2. AcOH, MeOH, 78% (two steps), *E/Z* > 25:1, *anti/syn* > 25:1); g) Dudley reagent (**25**), MgO, PhCF₃, 57%; h) LiOH, MeOH/THF/H₂O (2:2:1), 90%; i) TFA, CH₂Cl₂, 77%. Bn = benzyl, brms = based on recovered starting material, DIPEA = diisopropylethylamine, Dudley reagent = 2-benzyloxy-1-methylpyridinium triflate, SEM = 2-(trimethylsilyl)ethoxymethyl, TFA = trifluoroacetic acid.

27 as a suitable target for a formal synthesis since it had been converted into the natural product in two steps by a Yamaguchi macrolactonization and subsequent debenzylolation.^[24] The synthesis commenced with commercially available β -hydroxy ester **19** (Scheme 4). After protection using SEMCl, reduction, and carbamoylation, compound **20** was deprotonated with *s*BuLi/(+)-sparteine-surrogate and trapped with Bu₃SnCl 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 seco 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 β -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-*anti*-diols with excellent yields and diastereoselectivity. Related *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 (–)-decastrictine D. Additional applications of this efficient and highly stereoselective methodology in natural product synthesis are underway.

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