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Asymmetric Synthesis of Tertiary and Quaternary Allyl- and Crotylsilanes via the Borylation of Lithiated Carbamates

Varinder K. Aggarwal,* Michael Binanzer, M. Carolina de Ceglie, Maddalena Gallanti, Ben W. Glasspoole, Stephanie J. F. Kendrick, Ravindra P. Sonawane, Ana Vázquez-Romero, and Matthew P. Webster

School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, U.K.

v.aggarwal@bristol.ac.uk

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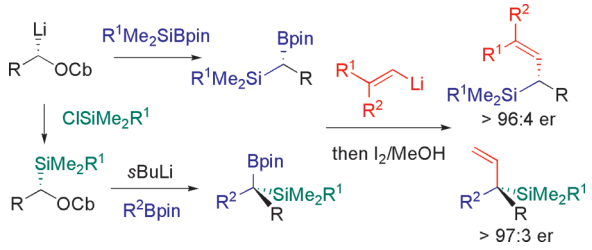
ABSTRACT



Tertiary allyl- or crotylsilanes have been prepared in high er and dr via the lithiation−borylation reaction of alkyl carbamates with silaboronates. Using a related strategy, quaternary allylsilanes could be accessed in similarly high er.

Allylsilanes are highly versatile synthetic intermediates which have been used extensively in complex molecule synthesis.[1] As such, methods to generate allylsilanes in high enantiomeric and diastereomeric purity have attracted widespread attention from the synthetic community.[2−8]

Methods for the preparation of *tertiary* allylsilanes have included Cu-catalyzed allylic alkylation[2,3] and carbonyl allylation.[4] Methods for the preparation of the more challenging *quaternary* allylsilanes have included the hydroboration[5] or hydrozirconation[6] of allenylsilanes followed by addition to aldehydes or imines, Claisen rearrangement of vinyl silanes,[7] Cu-catalyzed asymmetric allylic alkylation,[2] and enantioselective allylic substitution.[8] While many of these methods provide efficient pathways to specific allylsilanes, general strategies to allylsilanes in high er and dr, particularly in the case of crotylsilanes, remain underdeveloped.

(1) (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293–1316. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192. (c) Sarkar, T. K. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Thieme: Stuttgart, 2002; Vol. 4, pp 837−926.

(2) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554–4558.

(3) (a) Schmidtmann, E. S.; Oestreich, M. *Chem. Commun.* **2006**, 3643–3645. (b) Vyas, D. J.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8513–8515.

(4) Han, S. B.; Gao, X.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 9153–9156.

(5) (a) Wang, K. K.; Gu, Y. G.; Liu, C. *J. Am. Chem. Soc.* **1990**, *112*, 4424–4431. (b) Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1693–1696. (c) Lambert, W. T.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5501–5504.

(6) Wipf, P.; Pierce, J. G. *Org. Lett.* **2005**, *7*, 3537–3540.

(7) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529–1532.

(8) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315–14320.

(9) An alternative to Zweifel olefination is Suzuki−Miyaura cross-coupling of boronate esters with vinyl halides. However, whilst 1,1-silaboronic acid, $Me_3SiCH_2B(OH)_2$, couples with vinyl halides to give allylsilanes [see: (a) Zou, G.; Reddy, Y. K.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 7213–7215.] the more substituted 1,1-silaboronic acid pinacol esters do not [see:(b) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033–11035.] and so this strategy cannot be used to make tertiary or quaternary allylsilanes. Endo *et al.* did report the successful coupling of substituted 1,1-bisboronic acid pinacol esters. Apart from this and other isolated cases, secondary boronic acids/pinacol esters do not normally undergo efficient Suzuki−Miyaura cross-coupling. For a review, see: (c) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704–6716.

(10) (a) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 3652–3653. (b) Evans, D. A.; Crawford, T. C.; Thomas, R. C.; Walker, J. A. *J. Org. Chem.* **1976**, *41*, 3947–3953. (c) Matteson, D. S. In *The Chemistry of the Metal-carbon Bond*, Hartley, F. R., Ed.; Wiley: 1987; Vol. 4, pp 307−499 and references therein. (d) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535–1551.

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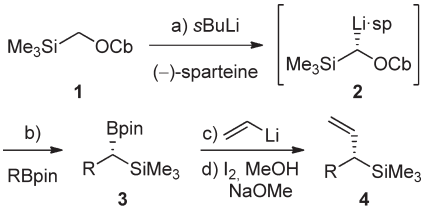
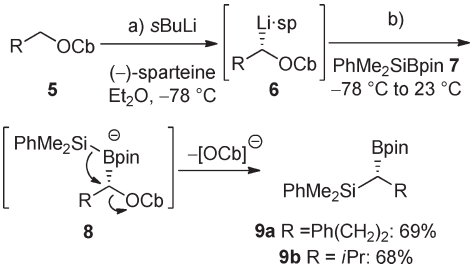
Scheme 1. Proposed Synthesis of Tertiary Allylsilanes[a]



[a] Cb = 2,2-diisopropylcarbamoyl, sp = (−)-sparteine, pin = pinacolato.

Scheme 2. Silaboration of Lithiated Carbamates **6**



Herein, we report two general strategies for the efficient preparation of both tertiary and quaternary allylsilanes in high er and dr using our lithiation−borylation method coupled with Zweifel olefination of the derived boronate esters.[9,10]

We previously reported that enantioenriched lithiated alkyl carbamates could react with boranes and boronate esters to give their homologated counterparts in high er.[11] This reaction could even be applied to β-silyl vinylboranes, which led to an asymmetric synthesis of β-hydroxy allylsilanes.[11d,e] Initial studies (Scheme 1) aimed to extend this approach to the synthesis of allylsilanes from α-silyl carbamate **1**, however, proved unrewarding, because the intermediate silyl-substituted lithiated carbamate **2** was configurationally unstable and led to racemic allylsilane **4**.[12]

We therefore considered an alternative approach: the reaction of a configurationally stable, alkyl-substituted lithiated carbamate **6**[13] with silaboronate **7**.[14] This was expected to give an intermediate ate-complex **8**, which would subsequently undergo 1,2-metalate rearrangement, involving migration of the silyl group with expulsion of the nucleofugal carbamate group, to furnish the 1,1-silaboronate **9**. While the migration of a carbon substituent is relatively common, there are only sporadic examples of the migration of a silyl group.[15] Nevertheless, this strategy ultimately proved to be successful (Scheme 2). Lithiation of carbamates **5**, followed by the addition of the commercially available boronate **7** and warming gave silaboronates **9a** and **9b** in 69% and 68% yield, respectively.

Conditions for the Zweifel olefination[10] had to be modified to obtain good yields due to the sensitive nature of the allylsilane product toward excess I_2. In fact, we found that I_2/MeOH was superior to the more commonly employed conditions of I_2/NaOMe/MeOH. As illustrated by the data summarized in Table 1, subsequent reaction of boronate esters **9** with the alkenylmetal reagents **10**[16] at −78 °C, followed by the addition of iodine in methanol, gave allylsilanes **11** in excellent er (97:3−94:6) and good to excellent yield (60−94%). Moreover, the dr was essentially perfect for entries 2, 3, and 6, giving the respective crotylsilanes as single diastereomers by ^{1}H NMR spectroscopy (dr >25:1). Only in the case of the highly hindered *Z*-crotylsilane **11e** (entry 5) was the *E*-diastereomer visible by NMR (85:15 dr in the crude material and 95:5 dr in the isolated product). In this case, the minor *E*-olefin presumably arises from the severe steric encumbrance of the conformation required for *anti*-elimination (leading to the *Z*-configuration) and so some *syn*-elimination occurs which leads to the small amount of the *E*-isomer observed (Scheme 3).[17]

It should be noted that, in the case of boronate ester **9a** (R = $PhCH_2CH_2$), vinylmagnesium bromide was sufficiently nucleophilic to effect ate-complex formation but, for the more hindered boronate ester **9b** (R = *i*Pr), the more reactive vinyllithium was required. Propenyllithium compounds were used due to their ease of preparation from the respective propenyl bromides by halogen−metal exchange.[16]

(11) (a) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7491–7494. (b) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778–782. (c) Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6317–6319. (d) Binanzer, M.; Fang, G. Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 4264–4268. (e) Robinson, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6673–6675. (f) Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 4025–4028.

(12) Our attempts to effect the lithiation−borylation reaction, shown in Scheme 1, only gave racemic allylsilane **4** (R = Ph) even when the reaction was conducted at −100 °C. The configurational instability of silyl-substituted lithiated carbamates has been noted before: (a) Simov, B. P.; Rohn, A.; Brecker, L.; Giester, G.; Hammerschmidt, F. *Synthesis* **2004**, *16*, 2704–2710. (b) Schweifer, A.; Hammerschmidt, F. *Tetrahedron* **2008**, *64*, 7605–7610.

(13) For reviews, see: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282–2316. (b) Hoppe, D.; Marr, F.; Brüggemann, M. In *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Springer-Verlag: Berlin, 2003; Vol. 5, pp 61−137 and references therein. (c) Hoppe, D.; Christoph, G. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2004; Part 2, pp 1055−1164.

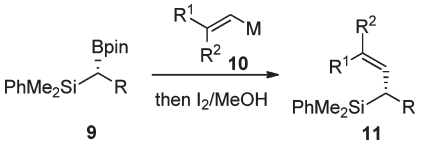
(14) Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **2000**, *19*, 4647–4649. In addition to it being commercially available (and easy to make according to the Suginome procedure), the UV chromophore present makes it especially useful in determining er and therefore better than the Me_3Si analogue.

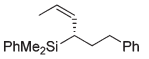
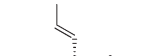
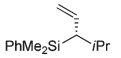
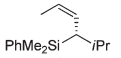
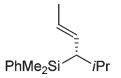
(15) (a) The silaboration has been pioneered by Buynak using ethyl diazoacetate as the carbenoid: Buynak, J. D.; Geng, B. *Organometallics* **1995**, *14*, 3112–3115. (b) Hata, T.; Kitagawa, H.; Masai, H.; Kurahashi, T.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 790–792. (c) Shimizu, M.; Kurahashi, T.; Kitagawa, H.; Shimono, K.; Hiyama T. *J. Organomet. Chem.* **2003**, *686*, 286–293.

(16) Preparation of vinyllithium: (a) Gassman, P. G.; Valcho, J. J.; Proehl, G. S.; Cooper, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 6519–6526. Preparation of propenyllithium:(b) Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, *52*, 4839–4842. (c) See Supporting Information of: Gérard, E. M. C.; Bräse, S. *Chem.—Eur. J.* **2008**, *14*, 8086–8089.

(17) (a) Matteson, D. S.; Liedtke, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 1526–1531. (b) Negishi, E.; Lew, G.; Yoshida, T. *J. Org. Chem.* **1974**, *39*, 2321–2322. (c) Slayden, S. W. *J. Org. Chem.* **1982**, *47*, 2753–2757. (d) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535–1551.

Table 1. Olefination of Silaboronates **9**[a]



	R (**9a,9b**)	reagent (**10**)[b]	product (**11a-f**)	yield (%)[c]	er[d]	dr[e]
1	$Ph(CH_2)_2$			81	97:3	
2	$Ph(CH_2)_2$			84	97:3	>25:1
3	$Ph(CH_2)_2$			94	97:3	>25:1
4	*i*Pr			60	96:4[f]	85:15
5	*i*Pr			80	96:4	95:5[g]
6	*i*Pr			80	96:4	>25:1

[a] Reactions were performed on 0.2−1.0 mmol scales. Boronate ester (1 equiv), alkenylmetal reagent (4 equiv), and methanolic I_2 (4 equiv), THF, −78 to 0 °C. [b] The alkenyllithium reagents were prepared from the respective alkenyl bromides using 2 equiv of *t*BuLi (see Supporting Information). [c] Yield of the isolated product. [d] The er was determined by HPLC analysis, using a chiral stationary phase, of the products derived from hydroboration/oxidation or from hydrogenation/Fleming−Tamao oxidation (see Supporting Information). [e] Determined by analysis of 400 MHz ^{1}H NMR spectra of the crude products. [f] Absolute stereochemistry was assigned after comparison with the literature.[2] All other assignments were made by analogy. [g] The dr was determined after column chromatography.

We were especially interested to see if we could extend this method to the significantly more challenging quaternary allylsilanes. To achieve this, we returned to the strategy described in Scheme 1 since we recognized that *secondary* silyl-substituted lithiated carbamates were configurationally stable at low temperature.[18] Our sequence commenced with lithiation and silylation of carbamate **5a** as previously described (Table 2).[18] Subsequent deprotonation with *s*BuLi/TMEDA followed by the addition of a boronate ester gave intermediates **18** with a unique 1,1-silaboronate quaternary stereogenic center. These intermediates could be either isolated in excellent yield (88−94% yield) or subjected to the next transformation *in situ* without prior workup. Brief optimization of the stoichiometry of the reagents, temperature, and time provided a set of conditions under which allylsilanes **19** were obtained in 62−75% yield and very high er (97:3−98:2) from carbamates **14** in one pot over two steps.

Several points are worthy of note. (i) The one-pot reaction gave a slightly higher yield compared to the two-step procedure. (ii) The corresponding *i*Pr substituted substrate was sterically too hindered for deprotonation with *s*BuLi under these conditions. (iii) For substrates **18**, the more reactive vinyllithium had to be used and the

(18) (a) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394–396. (b) Behrens, K.; Fröhlich, R.; Meyer, O.; Hoppe, D. *Eur. J. Org. Chem.* **1998**, 2397–2403.

Scheme 3. Proposed Origin of the Minor *E*-Crotylsilane **11f**

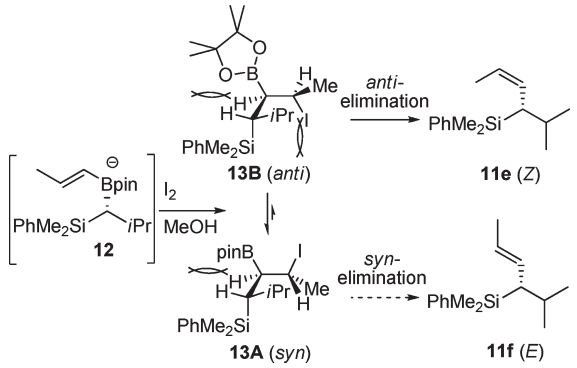
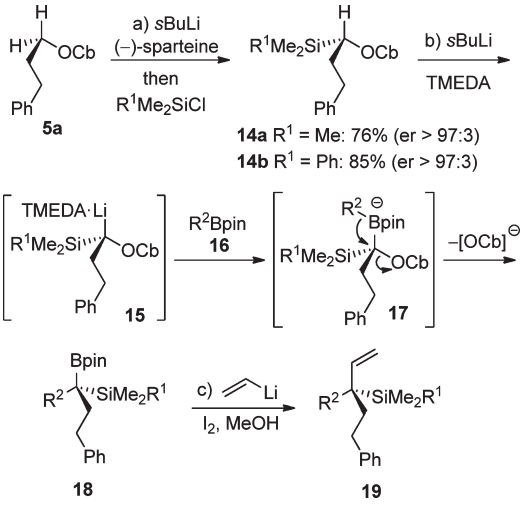


Table 2. Synthesis of Quaternary Allylsilanes **19**[a]



	R^1	R^2	yield of **18** (%)[b]	yield of **19** from **18** (%)[b]	yield of **19** from **14** (one pot, %)[b]	er[c]
1	Me	Me	88[d] (**18a**)		68 (**19a**)	98:2
2	Me	Et	94 (**18b**)	73 (**19b**)	75 (**19b**)	97:3[e]
3	Ph	Me	52[f] (**18c**)	73 (**19c**)		97:3
4	Ph	Et	76 (**18d**)	60 (**19d**)	62 (**19d**)	97:3

[a] Reagents and conditions: (i) *s*BuLi, TMEDA, Et_2O, −78 °C, 5 h then RMe_2SiCl. (ii) R^2Bpin, −78 to 23 °C or reflux. (iii) Vinyllithium (2 equiv, prepared from tetravinyltin and *n*BuLi, THF, 0 °C), THF, 0 °C then I_2/MeOH. TMEDA = *N,N,N′,N′*-tetramethylethylenediamine. [b] Yield of isolated product. [c] The er was determined by HPLC analysis, using a chiral stationary phase, of the products derived from hydroboration/oxidation. [d] Racemic substrate was used for this reaction. [e] The absolute stereochemistry was assigned by X-ray analysis of the alcohol obtained from **19b** by hydroboration/oxidation. All other assignments were made by analogy (see Supporting Information for details). [f] $MgBr_2$ was added to promote the 1,2-metalate rearrangement. Reflux conditions led to partial racemization presumably due to reversibility of the ate-complex formation.

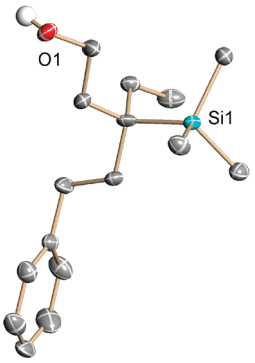


Figure 1. X-ray structure of the alcohol obtained from hydroboration/oxidation of allylsilane **19b**.

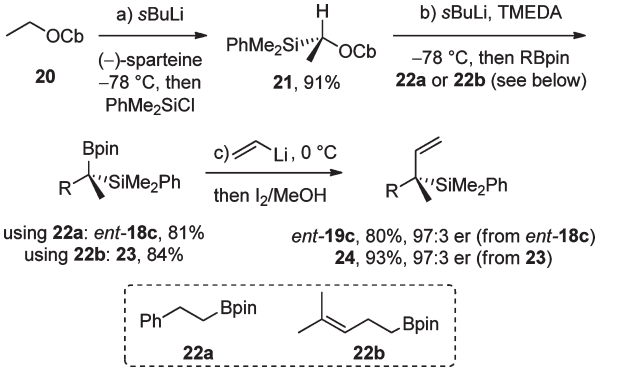
temperature raised to 0 °C for efficient ate-complex formation. The vinyl Grignard reagent only gave low conversions. (iv) Reaction of **18** with propenyllithium reagents led to incomplete formation of the ate-complex, presumably due to the severe steric bulk of these 1,1-silaboronates. (v) The absolute stereochemistry was determined by X-ray analysis of the alcohol obtained by hydroboration/oxidation of allylsilane **19b** (see Figure 1 and Supporting Information).[19] (vi) This process could be extended to the phenyldimethylsilyl group, enabling the incorporation of a further synthetic handle.

One advantage of this approach is that either enantiomer of the intermediate boronate ester or the product allylsilane can be obtained simply by switching the groups on the carbamate and the boronate ester, thus obviating the need to use the (+)-sparteine surrogate.[20] *ent*-**19c** was synthesized starting from ethyl diisopropyl carbamate **20** (Scheme 4). Deprotonation using *s*BuLi/(−)-sparteine followed by addition of phenyldimethylsilyl chloride gave organosilane **21**. Subsequent lithiation using *s*BuLi/TMEDA followed by the addition of boronate ester **22a** gave, after 1,2-metalate rearrangement, the intermediate

(19) CCDC 800290 contains the supplementary crystallographic data for the alcohol obtained from allylsilane **19b** by hydroboration/oxidation. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(20) McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378–16379.

Scheme 4. Synthesis of *ent*-**19c**



boronate ester *ent*-**18c** in excellent yield. Olefination with vinyllithium and methanolic iodine gave allylsilane *ent*-**19c** in 80% yield and 97:3 er.

The scope of the reaction was further exemplified in the synthesis of allylsilane **24**, bearing the ubiquitous prenyl group, using the commercially available boronate ester **22b**; excellent yields and er were observed throughout.

In summary, we have developed a simple method for the synthesis of tertiary allyl- or crotylsilanes in high er and dr using the lithiation−borylation reaction of alkyl carbamates with silaboronates. Using a related strategy, we have developed a unique reaction sequence that leads to quaternary allylsilanes in similarly high er.

Acknowledgment. We thank the EPSRC for support of this work. V.K.A. thanks the Royal Society for a Wolfson Research Merit Award and the EPSRC for a Senior Research Fellowship. We thank Inochem − Frontier Scientific for generous donation of boronic acids and boronate esters. We thank Dr. Mairi Haddow (School of Chemistry University of Bristol, UK) for X-ray analysis. B.W.G. thanks Queen's University for a Doctoral Travel Grant. A.V.-R. thanks IRB Barcelona and MICINN for a travel bursary.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.