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Strategic Trimethylsilyldiazomethane Insertion into pinB−SR Followed by Selective Alkylations

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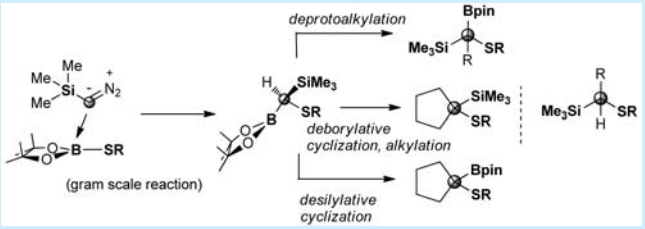
Supporting Information

ABSTRACT: The insertion of the diazo derivative Me_3SiCHN_2 into pinB−SR σ bonds (R = Ph, Tol, Bn) allows a direct synthesis of multisubstituted H−C(SR)(Bpin)($SiMe_3$) compounds. Consecutive base-assisted transformations of HC(S)(B) (Si) systems lead to deborylative alkylations, Sommelet−Haüser rearrangements, and deprotoalkylations. Intramolecular cyclizations can be selectively performed either via desilylative or deborylative manifolds by fine-tuning the base employed.



Among the transformations based on the insertion of diazo derivatives into a σ bond of interelement species,[1] the use of boron-containing reagents affords a valuable synthetic strategy toward the preparation of unprecedented organoboranes. In particular, the B−H, B−Cl, and B−C species have become suitable reagents for metal-catalyzed or uncatalyzed α,α-substitution of diazo compounds.[2,3] Amid the diazo compound derivatives, trimethylsilyldiazomethane (Me_3SiCHN_2) appears also as a convenient reagent, since upon insertion, the α-$SiMe_3$ functional unit is introduced.[4−6] The insertion of diazo compounds into B−B bonds has been successfully developed through Pt-catalyzed reactions, opening a new strategy toward 1,1-diboration protocols.[7]

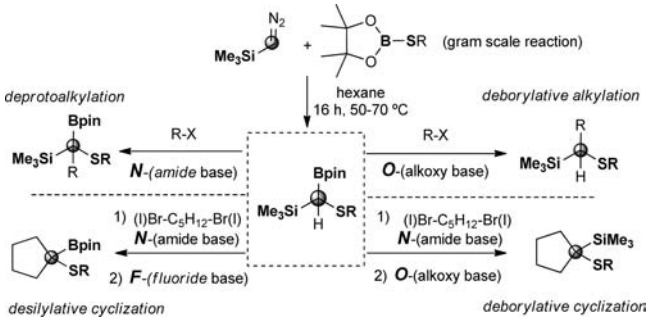
The in situ generation of nonstabilized diazo compounds by thermal decomposition of *N*-tosylhydrazone salts has become an alternative method to promote the metal-free insertion of diazoalkanes into H−Bpin (Bpin = pinacolboryl), Me_2PhSi−Bpin, and pinB−Bpin.[8] In the last year, our group developed the insertions of nonstabilized diazo compound into the σ B−B bond of the nonsymmetric diboron reagent pinB−Bdan (Bdan = 1,8-naphthalenediaminoboryl).[9]

With all these precedents in mind, we became interested in developing a method for the insertion of the diazo compound Me_3SiCHN_2 into B−S bonds to promote a direct synthesis of main group, multisubstituted sp^3 carbons (Si, B, S). We envisage that these compounds could help to increase structurally diverse molecules of synthetic potential since subsequent base-mediated functionalizations via deborylative alkylation, Sommelet−Haüser rearrangement, and deprotoalkylation can be developed. Selective intramolecular deborylative or desilylative cyclizations are also reported here (Scheme 1).

To verify experimentally the above hypothesis, we started the study by exploring the insertion of the commercially available Me_3SiCHN_2 into PhS−Bpin (**1a**) (which was prepared by Rh-catalyzed dehydrogenative borylation of PhSH with 1 equiv of the borane H−Bpin, at room temperature).[10] Through initial experiments, it was found that an excess of the diazo compound (diazo/borane = 2/1) was beneficial for the reaction completion. The insertion reaction proved amenable to gram scale just by stirring a mixture of 2 M hexane solution of the Me_3SiCHN_2 and the borane at 50 °C for 6 h. Under these conditions, 94% of **2a** can be isolated (Scheme 2). Following the same method, the insertion of Me_3SiCHN_2 was extended to TolS−Bpin (**1b**) and BnS−Bpin (**1c**). These reactions gave rise to similar high isolated yields of the corresponding **2b** and **2c**, although 70 °C and 16 h were required (Scheme 2).

The mechanism of the insertion of the diazo reagent into the interelement B−S σ bond, might be understood as an initial interaction of the nucleophilic diazo carbon to the electron

Scheme 1. Strategic Trimethylsilyldiazomethane Insertion into pinB-SR, Followed by Selective Alkylation Methods Carried out in This Work



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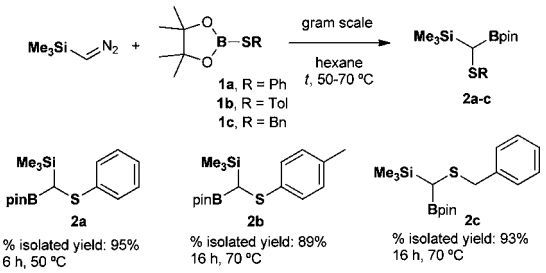
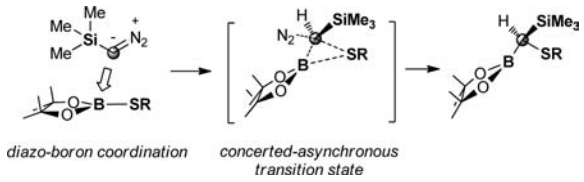
Scheme 2. Optimized Reaction Conditions for the Metal-Free Insertion of Me_3SiCHN_2 into PhS−Bpin, TolS−Bpin, and BnS−Bpin



deficient boron of the Bpin moiety, followed by the 1,2-migration of the adjacent SR moiety to yield the α,α-substituted product and the concomitant release of dinitrogen (Scheme 3). A similar

Scheme 3. Suggested Mechanism for the Insertion of Me_3SiCHN_2 into RS−Bpin

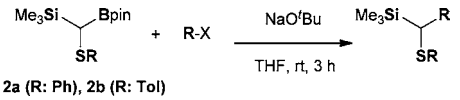


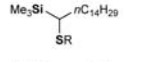
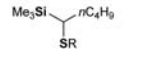
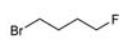
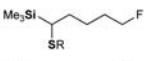
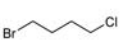
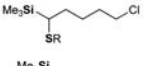
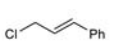
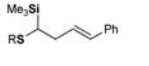
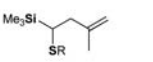
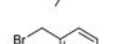
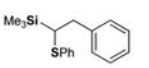
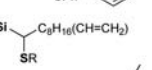
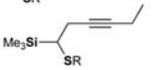
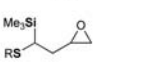
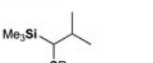
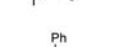
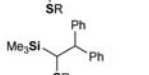
mechanism was already postulated by DFT calculations using pinB−Bpin or pinB−Bdan and CH_3CHN_2 as the model diazoalkane, suggesting a concerted, yet asynchronous mechanism.[9]

The Lewis acidity of the Bpin moiety in the RS−Bpin reagents seems to be responsible for the insertion reaction but also it might induce a deborylative alkylation sequence from products **2a−c**. If successful, this two-step sequence would constitute an unprecedented protocol for the synthesis of α-silyl sulfides. With the aim of carrying out the first attempt toward the deborylative alkylation, we selected product **2a** as the substrate and $nC_{14}H_{29}Br$ as the alkylating reagent. The presence of a base such as NaO^{t}Bu was required to promote the alkoxide-induced deborylation, as described for the generation of α-boryl carbanions from geminal (bis)boronates.[11,12] The reaction conditions entail the mixing of 1 equiv of $nC_{14}H_{29}Br$ with an excess of **2a** (1.3 equiv) in THF. An excess of **2a** versus the alkyl halide was used to discard any plausible decomposition along the reaction. Within 3 h, at room temperature, the α-silyl sulfide **3a** was observed in 84% yield (Table 1, entry 1). Longer reaction times did not provide any higher conversions. Very similar behavior was observed when **2b** reacted with $nC_{14}H_{29}Br$ to isolate **3b** in 68% yield (Table 1, entry 2).

Next, we conducted the deborylative alkylation of **2a** with 1-bromobutane. In this case, a 69% yield of the α-silyl sulfide product was isolated (Table 1, entry 3). When we explored the alkylation reaction of **2b** with nC_4H_9X (X = I, Br, Cl) we observed that 1-iodo- and 1-bromobutane reacted faster (64% and 83%, respectively), while the corresponding chloro derivative was only converted into the desired product in 19%. Hence, compound **2b** reacted with nC_4H_9I to give the higher conversion on **4b**, 80% isolated yield (Table 1, entry 4). The superior leaving group ability of a Br in the presence of chloro- or fluoroalkanes was exploited in the deborylative alkylation using $Br(CH_2)_4F$ and $Br(CH_2)_4Cl$. In both cases, the formation of a new C−C bond

Table 1. Substrate Scope of Deborylative Alkylation of Derivatives 2 via S_N2 Pathway[a]



entry	R-X	product	NMR yield (%)[b]	isolated yields [%]
1 2	$nC_{14}H_{29}Br$		**3a**, R = Ph, 84 **3b**, R = Tol, 73	65 68
3 4	nC_4H_9Br nC_4H_9I		**4a**, R = Ph, 69 **4b**, R = Tol, 83	56 80
5 6			**5a**, R = Ph, 84 **5b**, R = Tol, 67	81 61
7 8			**6a**, R = Ph, 73 **6b**, R = Tol, 89	71 87
9 10			**7a**, R = Ph, 80 **7b**, R = Tol, 87	74 80
11 12			**8a**, R = Ph, 85 **8b**, R = Tol, 62	78 ---
13 14			**9a**, R = Ph, 80 **9b**, R = Tol, 81	75 79
15 16	$(CH_2{=}CH)C_8H_{16}Br$		**10a**, R = Ph,71 **10b**, R = Tol,80	67 72
17 18			**11a**, R = Ph, 67 **11b**, R = Tol, 68	61 60
19 20			**12a**, R = Ph, 81 **12b**, R = Tol, 77	--- 42
21 22			**13a**, R = Ph, 71 **13b**, R = Tol, 75	68 67
23			**14a**, R = Ph, 40	15

[a]Reaction conditions: R−X (0.077 mmol), HC(Bpin)($SiMe_3$)(SR) (1.3 equiv), NaO^{t}Bu (4 equiv), THF (0.5 mL), at rt for 3 h. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with 1,4-dinitrobenzene or naphthalene as an internal standard, which was added after the reaction.

took place selectively at the C−Br site, leaving the C−F and the C−Cl bonds intact (Table 1, entries 5−8). However, S_N2-type alkylation of the more activated cinnamyl chloride was easily performed to form **7a** and **7b** (Table 1, entries 9 and 10). In this case, the S_N2 reaction of less reactive C−Cl is encouraged because the double bond stabilization in the transition state. In agreement with the last result, the deborylative alkylation of other reactive allylic systems was carried out to form α-silyl sulfides **8a** and **8b** in relatively high conversions (Table 1, entries 11 and 12). Similar values were observed for the deborylative alkylation of benzyl bromide, providing compounds **9a** and **9b**, up to 75% and 79% isolated yield, respectively (Table 1, entries 13 and 14). The compatibility of other functional groups with respect to the base-mediated deborylative alkylation was demonstrated with substrates containing double and triple bonds. In these cases, the corresponding products **10a**,**b** and **11a**,**b** were nicely formed without any effect to the unsaturated bonds (Table 1, entries 15−18). Even more notable is the example where the substrate featuring an epoxide ring resulted in an alkylated product where the epoxide functional group remained unaltered (Table 1, entries 19 and 20). We also conducted deborylative alkylation with secondary alkyl halides, and remarkably, we were able to isolate

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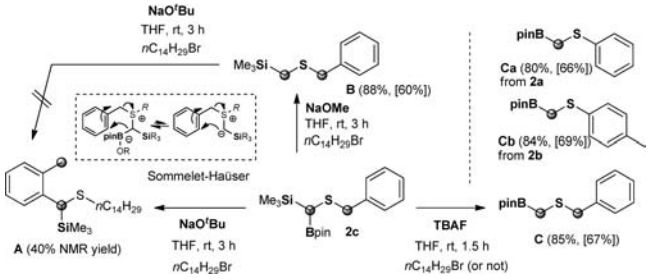
the corresponding geminal thiosilane products **13a** (R = Ph) and **13b** (R = Tol) in acceptable yields (Table 1, entries 21 and 22). The use of more sterically hindered secondary alkyl electrophiles, such as ^{i}Bu-I, can also be used. Interestingly, compound **14a** could also be isolated from the reaction media, demonstrating the generality of the substrate scope, even for the most challenging electronic and steric secondary alkyl halides (Table 1, entry 23).

The reaction of **2c** with nC$_{14}$H$_{29}$Br as electrophile and NaO^{t}Bu as base, proved to be more sluggish, affording mainly a constitutional isomer of the expected α-silyl sulfide. The new compound was identified as **A** (Scheme 4) and its formation could

Scheme 4. Deborylative Alkylation of 2c with NaOtBu and NaOMe; Desilylation of 2a−c with TBAF (% NMR Yields, [% Isolated Yields])

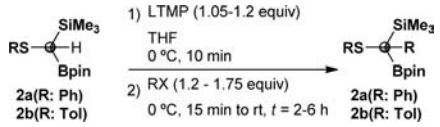


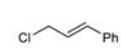
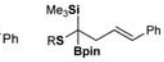
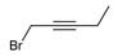
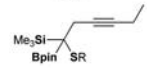
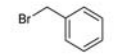
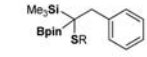
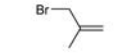
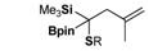
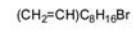
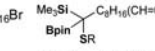
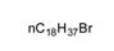
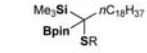
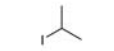
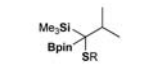
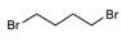
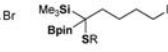
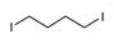
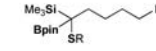
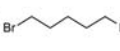
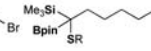
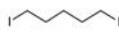
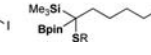
be explained as a result of a Sommelet−Haüser rearrangement, (an intramolecular [2,3]-sigmatropic rearrangement of a sulfonium salt to *ortho*-substituted benzyl sulfides by means of the treatment with a strong base).[13] This product was formed along with relative percentages of the expected alkylation sulfide (20%) and the protodeborylated product (11%, **B**); however, the similar polarity of the last two species hampered the proper isolation from the reaction mixture. The product **A** is most likely arising from substrate **2c** and not by the intermediacy of protodeborylated species **B**,[14] since a blank experiment from **B** carried out under the same reaction conditions, did not lead to product **A**. Unfortunately, all attempts to maximize the production of **A** have been unsuccessful.

Interestingly, the nature of the base demonstrated to be of crucial importance in these reactions, since only protodeborated compound **B** was principally formed (88% NMR yield and 60% isolated yield) when the reaction was performed with NaOMe instead of NaO^{t}Bu. Notably, when we exposed the substrate **2c** to a fluoride base (TBAF) and nC$_{14}$H$_{29}$Br as the model alkylating reagent, within 1.5 h at room temperature, the desilylated product **C** was the only product observed (85% NMR yield), neither alkylation[15] or rearrangement were detected (Scheme 4). The same reaction outcome was observed in the absence of the electrophile nC$_{14}$H$_{29}$Br, and the yield was the same. Such behavior seems to indicate a higher ability of the fluoride base to induce the selective functionalization of the Me$_3$Si group in the presence of the Bpin moiety.[16] This reactivity was extended to the multisubstituted systems **2a** and **2b** to produce **Ca** and **Cb** in high isolated yields (Scheme 4, right).

Next, we turned our attention to the S$_N$2 alkylations that involve α-boron and α-silyl-stabilized carbanions generated through deprotonation of the alkyl boronate esters **2**. Interestingly, the reaction between cinnamyl chloride and **2a** (2 equiv) in the presence of NaO^{t}Bu (3 equiv) in toluene at 50 °C produced exclusively compound **15a** that was isolated in 42% (Table 2, entry 1). As far as we are aware, this is the first example of this type of α-boryl deprotonation/alkylation reactions taking

Table 2. Substrate Scope of Deprotonation−Alkylation of Derivatives 2 via S$_N$2 Pathway[a]



entry	R-X	product	NMR yield (%)[b]	isolated yields [%]
1[c]			**15a**, R = Ph, 61	42
2			**15a**, R = Ph, 79	70
3			**15b**, R = Tol, 74	73
4			**16b**, R = Tol, 10	---
5			**17a**, R = Ph, 50	42
			17b, R = Tol, 40	37
6[d]			**18b**, R = Tol, 53	52
7[d]			**19b**, R = Tol, 40	30
8[d]			**20b**, R = Tol, 45	36
9[d]			**21b**, R = Tol, 45	43
10[e]			**22a**, R = Ph,69	64
			22b, R = Tol, 77	72
11[e]			**23a**, R = Ph, 83	67
			23b, R = Tol, 80	62
12[e]			**24b**, R = Tol, 80	72
13[e]			**25b**, R = Tol, 78	71

[a]Reaction conditions: **2** (0.2 mmol, 1 equiv), R−X (0.24 mmol, 1.2 equiv), LTMP (0.21 mmol, 1.05 equiv), THF, t = 2 h. [b]Yields were determined by ^{1}H NMR with 1,4-dinitrobenzene or naphthalene as an internal standard. [c]R-X (0.1 mmol, 1 equiv), **2a** (0.2 mmol, 2 equiv), NaO^{t}Bu (0.3 mmol, 3 equiv), toluene, 50 °C, t = 24 h. [d]**2b** (0.15 mmol, 1 equiv), R−X (0.19 mmol, 1.3 equiv), LTMP (0.18 mmol, 1.2 equiv), THF, t = 3 h. [e]**2b** (0.3 mmol, 1 equiv), R−X (0.52 mmol, 1.75 equiv), LTMP (0.35 mmol, 1.2 equiv), THF, t = 6 h.

place in the presence of an alkoxy base, in place of the commonly employed strong alkyl or amide lithium bases.[17] However, only when we used lithium 2,2,6,6-tetramethylpiperazide (LTMP),[18] compound **15a** was formed in up to 70% isolated yield (Table 2, entry 2). The reaction of cinnamyl chloride and **2b** also provided the product **15b** in 73% isolated yield (Table 2, entry 3). We extended the use of **2b** for further S$_N$2 deprotoalkylations. The reaction proved feasible with a series of substrates featuring allylic and benzylic systems, albeit in moderate yields (Table 2, entries 4−6). The alkylation is also compatible with the presence of a monosubstituted terminal double bond (Table 2, entry 7). Noteworthy is the use of more hindered secondary alkyl halides. In this case, the alkylation took place in a non-negligible 43% yield (Table 2, entry 9). With these encouraging results, we turned our attention to the use of dibromo and diiodo alkyl derivatives.[11] To prevent the incorporation of 2 equiv of the reagent **2**, a higher excess (1.75 equiv) of the electrophile was employed. The reaction proved to be quite efficient with those challenging

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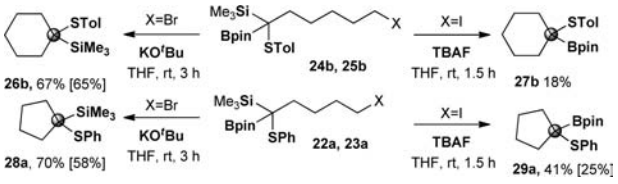
halides, giving rise exclusively to the monoalkylated product in good yields (Table 2, entries 10−13).

Finally, we were able to conduct a selective intramolecular deborylative cyclization in the presence of KO^{t}Bu at rt. The new 5- and 6-membered rings, **28a** and **26b**, respectively, were isolated in high yield (Scheme 5). Alternatively, when the base was TBAF at

Scheme 5. Selective Intramolecular Deborylative or Desilylative Cyclizations



rt, we were able to promote the desilylative cyclizations of **23a** and **25b** as a result of the preferential Si activation in the presence of the fluoride TBAF base. This last method opens the door to the synthesis of interesting α-functionalized aliphatic boronate esters.[19]

We have developed a new route to gain access to main group (Si, B, S) multisubstituted carbons that could help to increase structurally diverse molecules through selective functionalization of B and Si moieties by fine tuning the base.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01840.

Experimental procedures and spectral data for insertion of Me_3SiCHN_2 into pinB-SR, deborylative alkylation, selective protodesilylation, deprotonation/alkylation, deborylative cyclization, and desilylative cyclization (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ye, T.; McKervey, M. *Chem. Rev.* **1994**, *94*, 1091. (b) Candeias, N. R.; Paterna, R.; Gois, P. M. P. *Chem. Rev.* **2016**, *116*, 2937. (c) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, *2005*, 1479.

(2) (a) Neu, R. C.; Jiang, Ch.; Stephan, D. W. *Dalton Trans.* **2013**, *42*, 726. (b) Goddard, J. P.; Le Gall, T.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1455.

(3) (a) Chen, D.; Zhang, X.; Qi, W.-Y.; Xu, B.; Xu, M.-H. *J. Am. Chem. Soc.* **2015**, *137*, 5268. (b) Argintaru, O. A.; Ryu, D.; Aron, I.; Molander, G. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 13656. (c) Molander, G. A.; Ryu, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 14181.

(4) Moore, J. A.; Reed, D. E. *Org. Synth.* **1973**, 351.

(5) (a) Anderson, R.; Anderson, S. B. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; JAI Press: Greenwich, CT, 1991; Vol. *I*, p 303. (b) Shioiri, T.; Aoyama, T. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; JAI Press: Greenwich, 1993; Vol. *I*, p 51. (c) Shioiri, T.; Aoyama, T. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.: Wiley: Chichester, 1995; p 5248.

(6) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044.

(7) (a) Abu Ali, H.; Goldberg, I.; Srebnik, M. *Organometallics* **2001**, *20*, 3962. (b) Abu Ali, H.; Goldberg, I.; Kaufmann, D.; Burmeister, C.; Srebnik, M. *Organometallics* **2002**, *21*, 1870. (c) Wommack, A. J.; Kingsbury, J. S. *Tetrahedron Lett.* **2014**, *55*, 3163.

(8) (a) Li, H.; Wang, L.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2943. (b) Li, H.; Shangguan, X.; Zhang, Z.; Huang, S.; Zhang, Y.; Wang, J. *Org. Lett.* **2014**, *16*, 448.

(9) Cuenca, A. B.; Cid, J.; García-López, D.; Carbó, J. J.; Fernández, E. *Org. Biomol. Chem.* **2015**, *13*, 9659.

(10) (a) Westcott, S. A.; Webb, J. D.; McIsaac, D. I.; Vogels, C. M. WO Patent 2006/089402 A1, 2006. (b) Fernández-Salas, J. A.; Manzini, S.; Nolan, S. P. *Chem. Commun.* **2013**, *49*, 5829.

(11) (a) Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581. (b) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.

(12) For copper-catalyzed/promoted sp^3-C Suzuki−Miyaura coupling reaction of *gem*-diborylalkanes with nonactivated electrophilic reagents, see: Zhang, Z.-Q.; Yang, C.-T.; Liang, L.-J.; Xiao, B.; Lu, X.; Liu, J.-H.; Sun, Y.-Y.; Marder, T. B.; Fu, Y. *Org. Lett.* **2014**, *16*, 6342.

(13) For related silicon-assisted Sommelet−Haüser rearrangements, see: Tanzawa, T.; Ichioka, M.; Shirai, N.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2845.

(14) See the Supporting Information for details.

(15) Strictly anhydrous conditions were applied. This result indicates that fluoro-desilylative alkylation is a more challenging reaction when compared to the corresponding deborylative alkylation: Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 230.

(16) (a) Tsai, D. J. S.; Matteson, D. S. *Organometallics* **1983**, *2*, 236. (b) Cooke, M. P., Jr.; Widener, R. K. *J. Am. Chem. Soc.* **1987**, *109*, 931. (c) Kawachi, M.; Tani, A.; Shimada, J.; Yamamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 4222.

(17) (a) Matteson, D. S.; Moody, R. J. *J. Am. Chem. Soc.* **1977**, *99*, 3196. (b) Matteson, D. S.; Arne, K. *J. Am. Chem. Soc.* **1978**, *100*, 1325. (c) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20. (d) Pelter, A.; Singaram, B.; Williams, L.; Wilson, J. W. *Tetrahedron Lett.* **1983**, *24*, 623.

(18) Endo, K.; Hirokami, M.; Shibata, T. *J. Org. Chem.* **2010**, *75*, 3469.

(19) Knochel, P. *J. Am. Chem. Soc.* **1990**, *112*, 7431.

DOI: 10.1021/acs.orglett.6b01840
Org. Lett. 2016, 18, 3830−3833