Strategic trimethylsilyldiazomethane insertion into pinB-SR followed by selective alkylations.

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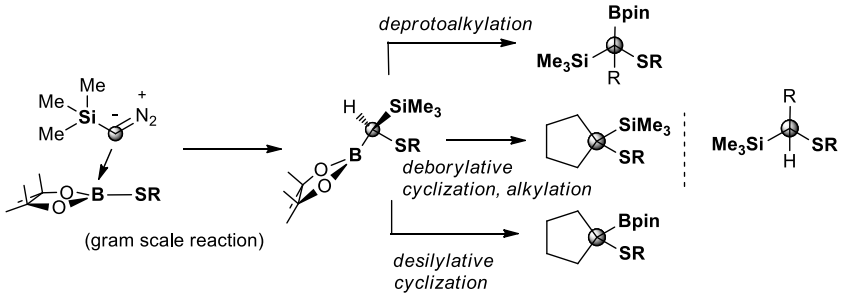


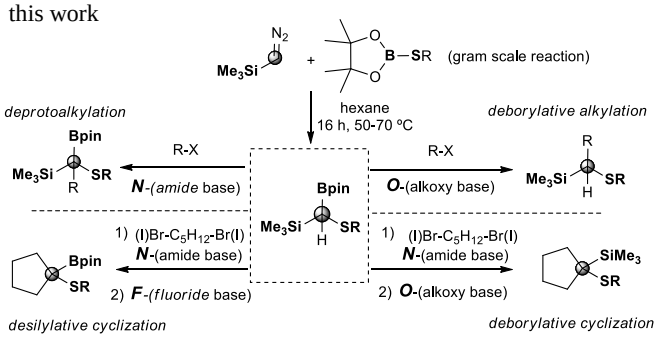
ABSTRACT: The insertion of the diazo derivative Me_3SiCHN_2 into pinB-SR sigma bonds (R = Ph, Tol, Bn), allows a direct synthesis of multisubstituted H-C(SR)(Bpin)($SiMe_3$) compounds. Consecutive base assisted transformations of HC(S)(B)(Si) systems lead to deborylative alkylations, Sommelet-Haüser 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 sigma 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.[4,5,6] The insertion of diazo compounds into B-B bonds has been succesfully developed through Pt-catalysed reactions, opening a new strategy toward 1,1-diboration protocols.[7]

The *in situ* generation of non-stabilized 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 non-stabilized diazo compound into the sigma B-B bond of the non-symmetric 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).

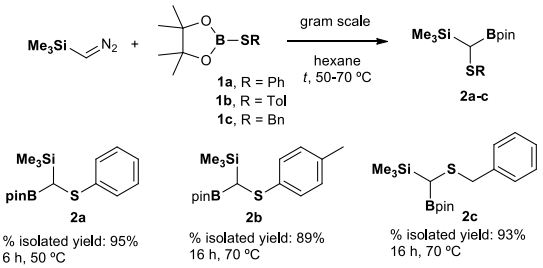
Scheme 1. Strategic trimethylsilyldiazomethane insertion into pinB-SR, followed by selective alkylation methods carried out in this work



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-catalysed dehydrogenative borylation of PhSH with one equivalent 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 ºC for 6 h. Under these conditions 94% of **2a** can be isolated (Scheme 3). Fol-

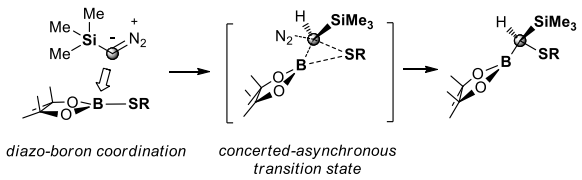
lowing the same method, the insertion of Me_3SiCHN_2 was extended to TolS-Bpin (**1b**) and BnS-Bpin (**1c**). These reactions gave rise to similar high isolated yields of the corresponding **2b** and **2c**, although 70 ºC and 16 h were required (Scheme 2).

Scheme 2. Optimized reaction conditions for the metal-free insertion of Me_3SiCHN_2 into PhS-Bpin, TolS-Bpin and BnS-Bpin.



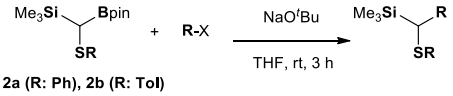
The mechanism of the insertion of the diazo reagent into the interelement B-S σ bond, might be understood as an initial interaction of the nucleophilic diazo carbon to the electron deficient boron of the Bpin moiety, followed by the 1,2-migration of the adjacent SR moiety to yield the α,α-substitued product and the concomitant release of dinitrogen (Scheme 3). A similar mechanism was already postulated by DFT calculations using pinB-Bpin or pinB–Bdan and CH_3CHN_2 as the model diazoalkane, sugesting a concerted, yet asynchronous mechanism.[9]

Scheme 3. Suggested mechanism for the insertion of Me_3SiCHN_2 into RS-Bpin

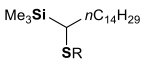
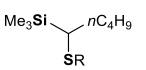
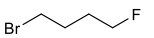
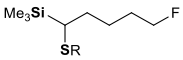
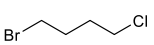
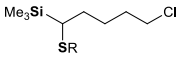
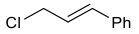
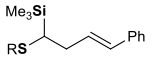
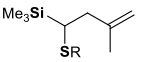
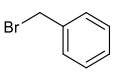
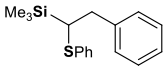
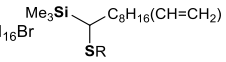
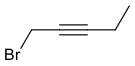
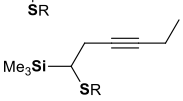
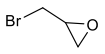
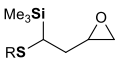
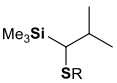
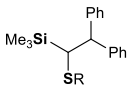


The Lewis acidity of the Bpin moiety in the RS-Bpin reagents seems to be responsible for the insertion reaction but also it might induce a deborylative alkylation sequence from products **2a-c**. If successful, this two-step sequence would constitute an unprecedented protocol for the synthesis of α-silyl 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 equivalent 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%, (Table 1, entry 1). Longer reaction time 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%, (Table 1, entry 2).

Table 1. Substrate scope of deborylative alkylation of derivatives **2** *via* S_N2 pathway[a]



2a (R: Ph), 2b (R: Tol)

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.

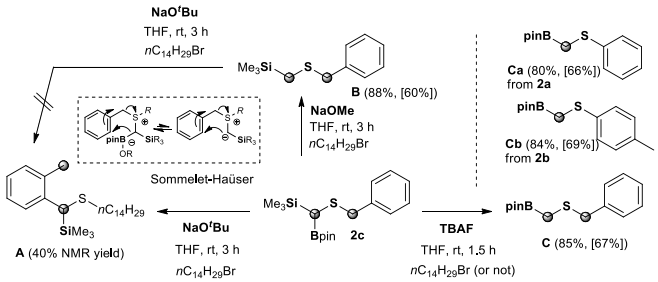
Next we conducted the deborylative alkylation of **2a** with 1-bromobutane. In this case, a 69% yield of the α-silyl sulfide product was isolated (Table 1, entry 3). When we explore the alkylation reaction of **2b** with nC_4H_9X (X = I, Br, Cl) we observed that 1-iodo and 1-bromobutane reacted faster (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 alkyla-

tion using Br-$(CH_2)_4$-F and Br-$(CH_2)_4$-Cl. In both cases, the formation of a new C-C bond 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 9-10). 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 relative high conversions (Table 1, entries 11-12). 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 13-14). 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 affect 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, entry 19-20). We also conducted deborylative alkylation with secondary alkyl halides, and remarkably we were able to isolate the corresponding geminal thiosilane products **13a** (R = Ph) and **13b** (R = Tol) in acceptable yields (Table 1, entries 21-22). The use of more sterically hindered secondary alkyl electrophiles, such as iBu-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 $n$$C_{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 5) and its formation could be explained as a result of a Sommelet-Haüser rearrangement, (an intramolecular [2,3]-sigmatropic rearrangement of a sulfonium salt to *ortho*-substituted benzyl sulphides 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.

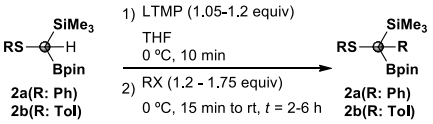
Interestingly, the nature of the base demonstrated to be of crucial importance in these reactions, since only protodeborated compound **B** was principally formed (88% NMR yield and 60% isolated yield) when the reaction was performed with NaOMe instead of NaO^{t}Bu. Notably, when we exposed the substrate **2c** to a fluoride base (TBAF) and $n$$C_{14}H_{29}Br$ as the model alkylating reagent, within 1.5 h at room temperature, the desilylated product **C** was the only product observed (85% NMR yield), neither alkylation[15] or rearrangement were detected (Scheme 4). The same reaction outcome was observed in the absence of the electrophile $n$$C_{14}H_{29}Br$, and the yield was the same. Such behaviour seems to indicate a higher ability of the fluoride base to induce the selective functionalization of the Me_3Si 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).

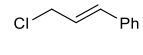
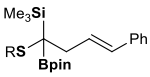
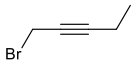
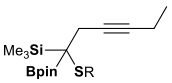
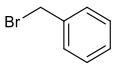
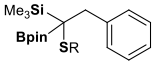
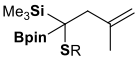
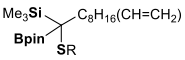
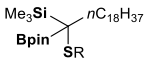
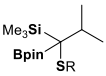
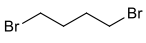
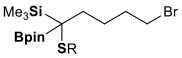
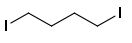
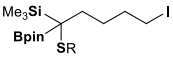
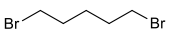
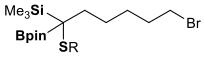
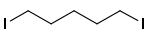
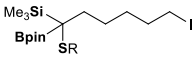
Scheme 4. Deborylative alkylation of 2c with NaOtBu and NaOMe. Desilylation of 2a-c with TBAF, (% NMR yields, [% isolated yields])



Next, we turned our attention to the S_N2 alkylations that involve α-boron and α-silyl stabilised 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 ºC, 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 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_N2 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 two equivalents 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 halides, giving rise exclusively to the mono-alkylated product in good yields (Table 2, entries 10-13).

Table 2. Substrate scope of deprotonation-alkylation of derivatives **2** *via* S_N2 pathway[a]

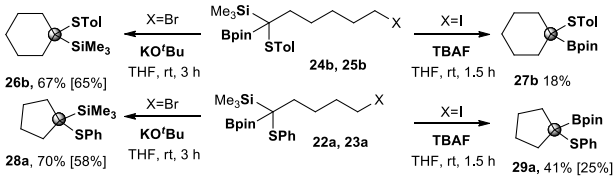


entry	R-X	product	NMR yield (%)[b]	isolated yields [%]
1[c]			**15a**, R = Ph, 61	42
2			**15a**, R = Ph, 79	70
3			**15b**, R = Tol, 74	73
4			**16b**, R = Tol, 10	---
5			**17a**, R = Ph, 50 **17b**, R = Tol, 40	42 37
6[d]			**18b**, R = Tol, 53	52
7[d]	$(CH_2{=}CH)C_8H_{16}Br$		**19b**, R = Tol, 40	30
8[d]	$nC_{18}H_{37}Br$		**20b**, R = Tol, 45	36
9[d]			**21b**, R = Tol, 45	43
10[e]			**22a**, R = Ph,69 **22b**, R = Tol, 77	64 72
11[e]			**23a**, R = Ph, 83 **23b**, R = Tol, 80	67 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 ºC, *t* = 24h, [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, 1equiv), R-X (0.52 mmol, 1.75 equiv), LTMP (0.35 mmol, 1.2 equiv), THF, *t* = 6 h

Finally, we were able to conduct a selective intramolecular deborylative cyclization, in the presence of KOtBu 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 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]

Scheme 5. Selective intramolecular deborylative or desilylative cyclizations.



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 and contains: 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.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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