Opportune *gem*-silylborylation of carbonyl compounds: to generate *in situ* selective tetrasubstituted olefins

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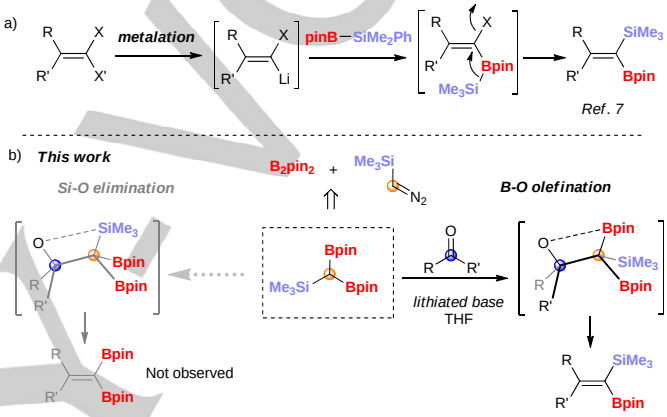
Dedication ((optional))

Abstract: The stereocontrol on the synthesis of tetrasubstituted alkenes can be predicted by the use of *gem*-silaborated structures that perform selective silicon based or boron based cross-coupling reactions. Iododesilylation becomes a strategic issue to accomplish the target C-Si cross coupling. The easy access to *gem*-silaborated olefins, from ketones and $HC(Bpin)_2(SiMe_3)$, is based on the strategic B-O olefination outcome.

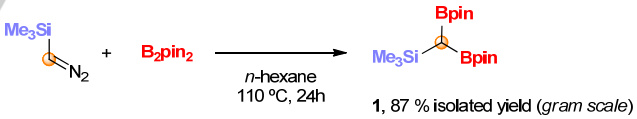
Geminally functionalized carbon atoms with Si-B interelement substituents represents a suitable transition-metal-free platform to prepare $C(sp^3)(B)(Si)$ compounds.[1] This reactivity was first observed by Buynak and Geng in 1995,[2] and is initiated by the interaction of ethyl diazoacetates with the empty *3p* orbital of the B atom in Me_2PhSi-Bcat (Bcat= catecholboryl moiety) forming an 'ate' complex. More recently, Wang and co-workers have revisited the subject providing the synthesis of 1-silyl-1-boryl compounds via reaction of the corresponding *N*-tosylhydrazones and $Me_2PhSiBpin$ (Bpin= pinacolboryl moiety) under thermal conditions.[3] Suginome, Ito et al., found that the insertion of alkyl and aryl isonitriles into the silicon-boron bond of silylboranes could also proceeded thermally to provide (boryl)(silyl)iminomethanes in moderate to good yields.[4]

Several interesting *gem*-silylborylations have been developed by reaction vinylic *gem*-dihalides with Me_2PhSi-Bpin in the presence of lithiated bases. This methodology, developed by Hiyama and Shimizu, affords 1-boryl-1-sylilalkanes,[5] 1-boryl-1-silylallenes,[6] and 1-boryl-1-sylilalkenes (Scheme 1a).[7] The latter example is of fundamental interest, since the access to *gem*-difunctionalization of alkenes becomes a direct method towards substituted olefins through stereodivergent protocols. In that context and considering our ongoing research based on metal-free insertions of diazo synthons into sigma non-symmetric B-B bonds[8] and B-S bonds,[9] we report here the straightforward insertion of the commercially available (trimethylsilyl)diazomethane into bis(pinacolato)diboron (B_2pin_2). The corresponding multisubstituted $HC(Bpin)_2(SiMe_3)$ product, can be eventually deprotonated in the presence of lithiated bases, generating a boron and silicon stabilised carbanion, able to attack a carbonyl function, as an attractive entry point to a Wittig-type olefination of carbonyl compounds. Upon such addition, two possible eliminations can take place: the classical Peterson-type Si-O elimination (Scheme 2b, left) to afford a *gem*-diboron product or the B-O elimination to access the *gem*-silaborated structures (Scheme 2b, right). Some previous examples about the feasibility of the stereoselective B-O *syn*-eliminations have been reported by Endo, Shibata and Morken.[10,11]



Scheme 1. Strategic synthesis to *gem*-silaborated alkenes.

The synthesis of $HC(Bpin)_2(SiMe_3)$ (**1**) can be efficiently obtained in a gram scale simply by mixing 1eq of B_2pin_2 and 2eq of (trimethylsilyl)diazomethane (2*M* hexane solution), heating the mixture at 110 ºC for 24h (87%, isolated yield, Scheme 2).[12]



Scheme 2. Direct access to $HC(Bpin)_2(SiMe_3)$ (**1**) in gram scale.

We tentatively examined the coupling reaction of **1** with cyclohexanone as model substrate, by adding lithium 2,2,6,6-tetramethylpiperidine (LiTMP) to **1**, in THF at 0 ºC, followed by addition of the cyclohexenone and subsequent warming up to room temperature for 2h. After the work up and chromatography, the *gem*-silylboronate product **2** was isolated in 95% (Table 1, entry 1). Similarly, excellent reactivity was exhibited by a series of 4-substituted cyclohexanones, affording the corresponding symmetric *gem*-silaborated alkenes **3**-**6** in very good yields (Table 2, entries 2-5). The use of 1.2 equiv of the base was found necessary, as the reaction proved to be less efficient when this amount was reduced to 1.0 equiv (Table 1, entry 6). Next, we applied the silylborylation protocol to 3-methylcyclohexanone. In this case a nearly quantitative formation of the *gem*-silylborylated product **7** took place (Table 2, entry 7), albeit as a 55:45 mixture of the two possible stereoisomers. Interestingly, 2-methylcyclohexanone lead to the

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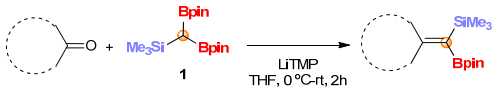
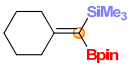
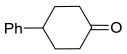
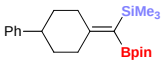
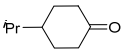
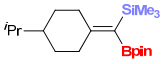
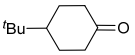
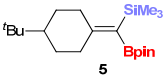
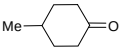
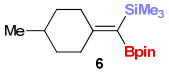
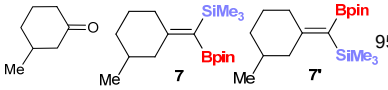
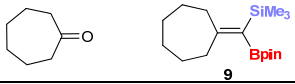
gem-dimetalated product **8** in 70% isolated yield and a synthetically useful 70:30 (*E*/*Z*) stereoisomeric ratio (Table 1, entry 8) in favour to the isomer with B close to the ortho-Me position (see SI for NOESY experiments). The protocol is also applicable to larger size cyclic ketones, such as cycloheptanone, providing the corresponding silylboronate product **9** in moderate isolated yield (Table 1, entry 9).

Table 1. *Gem*-silylborylation of cyclic ketones with **1**. [a]

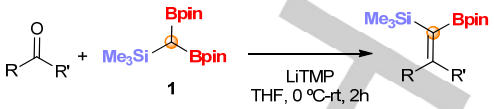


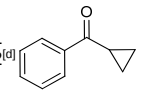
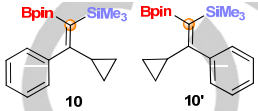
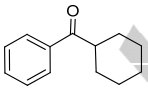
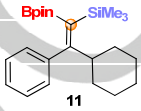
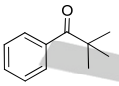
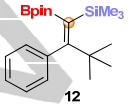
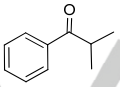
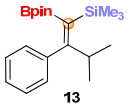
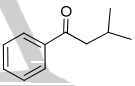
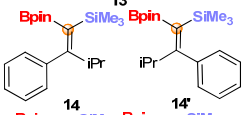
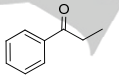
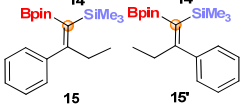
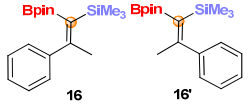
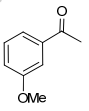
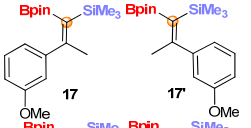
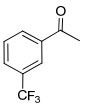
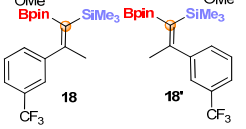
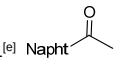
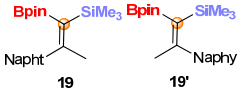
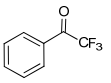
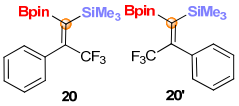
Entry	Substrate	Product	NMR yield (%)[b]	Isolated yields[%] (X/X')[c]
1		 **2**	97	95
2		 **3**	85	83
3		 **4**	89	87
4		 **5**	84	82
5 6[d]		 **6**	95 60	88 55
7	 **7** **7'**		95	90(55/45)
8	 **8** **8'**		75	70(70/30)
9	 **9**		60	56

[a]Reaction conditions: **1** (0.1 mmol, 1 equiv), ketone, (0.15 mmol, 1.5 equiv), LiTMP (0.12 mmol, 1.2 equiv), THF (0.2 mL), from 0 ºC to rt for 2h [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with naphthalene as an internal standard, which was added after the reaction. [c]Stereoisomeric Ratio. [d]**1** (0.1 mmol, 1 equiv), ketone, (0.1 mmol, 1equiv), LiTMP (0.1 mmol, 1equiv).

We next, explored the *gem*-silylborylation of non cyclic ketones and we found that cyclopropyl(phenyl)methanone was easily converted to the corresponding *gem*-silylboronate product regardless the amount of reagent **1** used (Table 2, entries 1,2). Interestingly, the reaction is performed with high stereoisomeric ratio (**10**/**10'** = 95/5) being the major isomer formed the one with the Bpin moiety *cis* to the Ph group (see SI for NOESY experiments).

Table 2. *Gem*-silylborylation of non-cyclic ketones with **1**. [a]

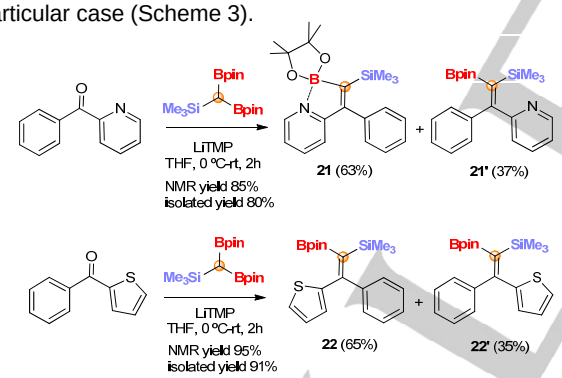


Entry	Substrate	Products	NMR yield (%)[b]	Isolated yields%] (X/X')[c]
1 2[d]		 **10** **10'**	92 93	87(95/5) 89(95/5)
3		 **11**	87	86(99/1)
4		 **12**	55	52(99/1)
5		 **13**	70	67(99/1)
6		 **14** **14'**	62	60(91/9)
7		 **15** **15'**	44	40(90/10)
8		 **16** **16'**	42	40(87/13)
9		 **17** **17'**	44	42(89/11)
10		 **18** **18'**	73	70(87/13)
11[e]		 **19** **19'**	53	50(88/12)
12		 **20** **20'**	92	91(63/37)

[a]Reaction conditions: **1** (1.2 equiv), ketone, (1 equiv), LiTMP (1.4 eq), THF (0.2 mL), from 0 ºC to rt for 2h [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with naphthalene as an internal standard, which was added after the reaction. [c]Stereoisomeric Ratio. [d]**1** (1 equiv), ketone, (1.5 equiv), LiTMP (1.2 equiv). [e]Napth= napthyl

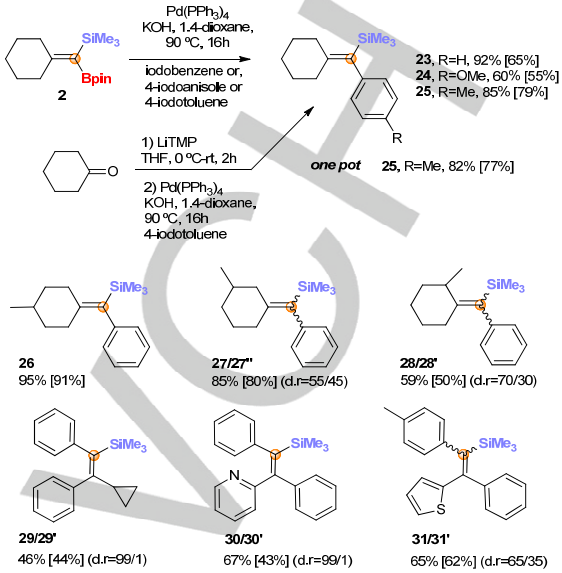
Even higher stereoselectivity has been observed in the reaction of hindered aliphatic ketones, such as cyclohexyl(phenyl)methanone, 2,2-dimethyl-1-phenylpropan-1-one and 2-methyl-1-phenylpropan-1-one, with a stereoisomeric

ratio up to 99/1 in products **11**, **12** and **13** respectively (Table 2, entries 3-5). The less sterically hindered ketone 2-methyl-1-phenylbutan-1-one was also conveniently converted into the desired *gem*-silylboronate product but the stereoisomeric ratio slightly decreased (**14/14'** = 91/9) (Table 2, entry 6). This trend is extended to the *gem*-silylborylation of aryl(ethyl)ketone and aryl(methyl)ketones, independently of the electronic nature of the substituents on the aryl group (Table 2, entries 7-11). It can be seen that the corresponding *gem*-silylboronate products **15**–**19** were prepared in stereoisomeric ratios about (**X/X'** = 87-90/13-10) with moderate yields except in the case of products **18/18'** that were isolated up to 70% probably due to the enhanced reactivity of the ketone as a consequence of the electron withdrawing meta-substituent in the aryl group (Table 2, entry 10). Similar criteria might justify the quantitative transformation of the phenyl(trifluoromethyl)ketone into the *gem*-silylboronate products **20/20'** (isolated yield 91%) despite the fact that the stereoisomeric ratio lowered to 63/37, (Table 2, entry 12). When phenyl(pyridin-2-yl)methanone was transformed into the *gem*-silylborated products **21/21'**, the stereoisomeric mixture was 63/37 being the major isomer **21** the one with Bpin moiety *cis* to the pyridine group. The stereoisomer **21** was easily separated and isolated in pure form from the stereoisomeric mixture due to the notable interaction between N and B, making the compound less polar (Scheme 3). Compound **21** showed a characteristic ^{11}B NMR signal at 18 ppm, as a consequence of the B-N interaction. In contrast, the *gem*-silylborylation of phenyl(thiophen-2-yl)methanone provided the mixture of the stereoisomeric silylborylated products **22/22'**, but **22** could not be separated from **22'** since the S-B interaction was not observed in this particular case (Scheme 3).



Scheme 3. *Gem*-silylborylation of phenyl(pyridin-2-yl)methanone and phenyl(thiophen-2-yl)methanone with **1**.

Our next challenge was to use the *gem*-silylboronated products in the selective generation of tetrasubstituted olefins and towards this end we initiated the study by conducting Suzuki-Miyaura cross-coupling of **2** with iodobenzene or 4-iodotoluene, in the presence of $Pd(PPh_3)_4$, KOH, 1,4-dioxane as solvent, at 90ºC during 16h,[13] as standard reaction conditions. The *gem*-silylboronated product **2** was efficiently transformed into 1-aryl,1-trimethylsilyl-methylenecyclohexane products **23**-**25** (Scheme 4). To our delight, we also proved that the straightforward transformation of cyclohexanone into **25** could also be performed in a "one pot" sequence, via *gem*-silylborylation followed by Pd-cross coupling, without the need to isolate the *gem*-silylboronated products (Scheme 4).

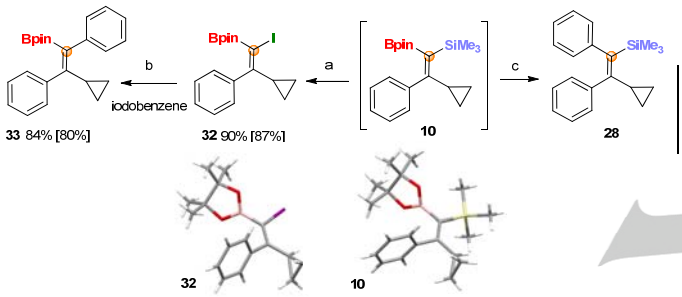


Scheme 4. Cross coupling of *gem*-silylborylated product **2** and sequential *one pot gem*-silylborylation / cross coupling of cyclehexenone.

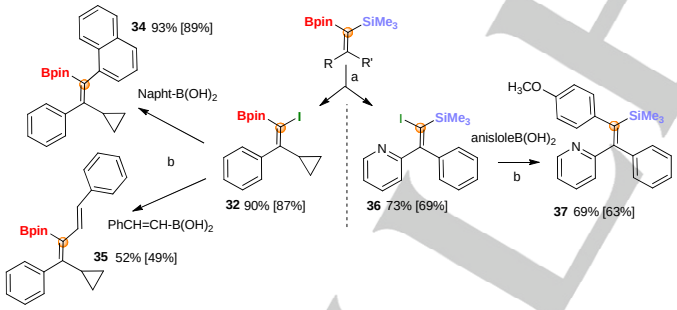
With this convenient approach in our hands, we applied the "one pot" sequence to a representative type of cyclic and non-cyclic ketones ketones. The *para*-methylcyclohexenone, followed the sequential one pot *gem*-silylborylation / cross coupling reaction providing the corresponding product **26** in high quantitative yield (Scheme 4). As expected, the *metha*- and *ortho*-methylcyclohexenones were transformed into **27/27'** and **28/28'** with lower stereoisomeric ratio (Scheme 4). However, the non-cyclic ketone cyclopropyl(phenyl)methanone was stereoselectively transformed into the trisubstituted 1-silylalkenes **29**, although yield was moderate (Scheme 4). We also were able to prove that the B-N interaction on the *gem*-silylboronated product **21** assisted the selective cross coupling from the stereoisomeric mixture **21/21'** since **30** was the exclusive product formed and no traces of **30'** were detected (Scheme 4). On the contrary, the lack of interaction between B and S in the intermediates **22/22'** did not assist the stereoselective C-C bond formation and therefore the *gem*-silylborylation / cross coupling reaction of phenyl(thiophen-2-yl)methanone only gave moderate stereoselection of the trisubstituted 1-silylalkenes **31/31'** (Scheme 4). This methodology complements the reported synthetic protocols based on the reactivity of alkylidene-type carbenoids with silylborane reagents followed by Suzuky-Miyaura cross coupling,[5] or iron catalyzed carbometalation ring opening of 1-trimethylsilylcyclopropenes,[14] or intramolecular *trans*-silylruthenation of internal alkynes and subsequent insertion of vinyl boronates[[5] to address the most challenging task of tetrasubstituted alkene synthesis.

The stereochemical course of the sequence of reactions has been established by X-Ray data of the intermediate *gem*-silylboronated product **10** (Scheme 5). Alternatively to the cross

coupling of **10** toward 1-silylalkene **28**, we also conducted the most challenging silicon based cross-coupling, keeping the Bpin unit untouched. We proceed via iododesilylation[16] of **10** with I_2 / $AgNO_3$ to obtain the desired product **32** with high yield, which was further reacted with $PhB(OH)_2$ in presence of Pd complex to access trisubstituted 1-borylalkene **33** with total control of stereoselectivity (Scheme 5). To the best of our knowledge, this is the first example of selective silicon based cross-coupling in silylboronated products and its usefulness rely in the synthesis and stereoselective control of unusual trisubstituted 1-borylalkenes, such as products **34** and **35**, which were isolated from the reaction of **32** with naphtylboronic esther and vinylboronic esther, respectively (Scheme 5). However, any attempt to iododesilylate the *gem*-silaborated product **21**, were unsuccessful and only the iododeborylated product **36** was observed, probably due to the interaction of N to B that assists the Bpin release (Scheme 5). The reactivity of 36 with $anisoleB(OH)_2$ allowed to isolate the trisubstituted 1-silylalkene **37** with total stereocontrol (Scheme 5).



Scheme 5. Stereochemical course of the sequential cross coupling via Suzuki-Miyaura and iododesilylation/cross coupling of **10**. [a]$AgNO_3$, I_2, 0ºC, 30 min; [b]$Pd(PPh_3)_4$, $RB(OH)_2$, TBAB, K_2CO_3, toluene, 90 ºC, 12h. [c]$Pd(PPh_3)_4$, KOH, 1,4-dioxane, 90 ºC, 16h; X-Ray diffraction structure of **10** and **32**.



Scheme 6. Divergent iododesilylation/cross coupling reactions. [a]$AgNO_3$, I_2, 0ºC, 30 min; [b]$Pd(PPh_3)_4$, $RB(OH)_2$, TBAB, K_2CO_3, toluene, 90 ºC, 12h.

Based on the new stepwise protocol to selectively functionalize the *gem*-silaborated products, we finally conducted the synthesis of tetrasubstituted olefins with total control of the stereoselectivity. To prove the concept, compound **38** was efficiently isolated from the reaction of **33** with 4-iodoanisole in presence of $Pd(PPh_3)_4$, and more remarkably, the challenging[17] all-carbon tetrasubstituted alkenes **39** and **40** were also generated from **34** and **35** via Pd mediated cross coupling with 4-iodoanisole and 4-$CF_3C_6H_4I$, respectively (Figure 1). Taking into consideration the success on the synthesis of the tetrasubstituted alkenes with full guarantee of the stereocontrol, we planned to apply it to the synthesis of Tamoxifen through the *gem*-silaborated compound **15**. As it can be seen in the scheme 7, the iododesilylation of **15** afforded compound **41** in 88% of isolated yield, which was further selectively submitted to cross coupling with IPh to form **42** in xx%. The last step concerns to the second cross coupling leading to the desired product Tamoxifen (**43**) in a decent yield.

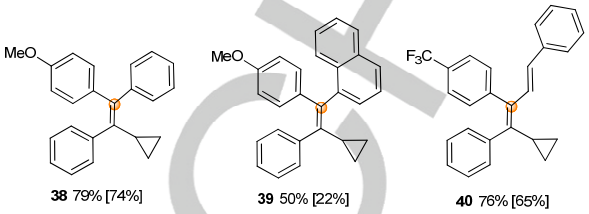
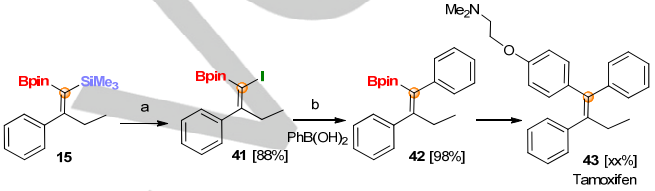


Figure 1. Synthesis of tretrasubstituted alkenes via *gem*-silaborated products



Scheme 7. Synthesis of Tamoxifen via *gem*-silaborated product **15**. [a]$AgNO_3$, I_2, 0ºC, 30 min; [b]$Pd(PPh_3)_4$, $RB(OH)_2$, TBAB, K_2CO_3, toluene, 90 ºC, 12h; [c]$Pd(PPh_3)_4$, RI, KOH, 1,4-dioxane, 90 ºC, 16h.

We conclude that $HC(Bpin)_2(SiMe_3)$ (**1**) can be efficiently prepared via insertion of (trimethylsilyl)diazomethane into B_2pin_2 and the subsequent formation of *gem*-silaborated products serve as the precursor of selective tetrasubstituted alkenes via selective silicon based or s boron based cross-coupling reactions. Total control of the selective substitution provides a systematic approach to all-carbon tetrasubstituted alkenes and Tamifoxen synthesis.

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Keywords: gem-silaborated products • insertion • iododesilylation • all carbon tetrasubstituted alkenes • tamoxifen

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Layout 2:

COMMUNICATION

Enrico LaCascia, Andrew Whting, Ana B. Cuenca*, Elena Fernández*

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Opportune *gem*-silylborylation of carbonyl compounds to generate *in situ* selective tetrasubstituted olefins

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