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Authors: Elena Fernández, Ana B Cuenca, and Enrico La Cascia

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Opportune *gem*-silylborylation of carbonyl compounds: a modular and stereocontrolled entry to tetrasubstituted olefins

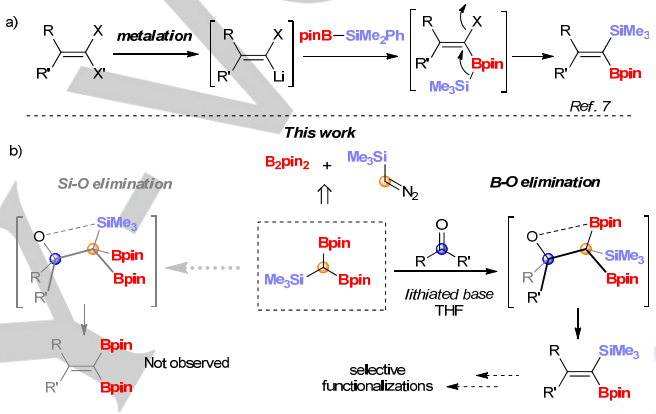
Enrico La Cascia, Ana B. Cuenca,* Elena Fernández*

Dedication ((optional))

Abstract: An easy access to highly versatile *gem*-silylboronate synthons is achieved by means of a new olefination reagent, H-C(Bpin)$_2$(SiMe$_3$). Subsequent silicon or boron-based selective functionalizations allow for modular and stereocontrolled synthesis of all-carbon tetrasubstituted alkenes. Particularly attractive to this approach is the iododesilylation reaction, which becomes a pivotal tool to C-Si functionalization.

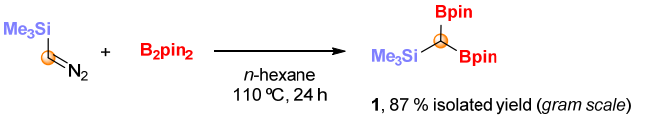
Geminally functionalized carbon atoms with Si-B interelement substituents represent a unique platform that combines two of the most versatile main group elements.[1] Among other methods,[2] the corresponding C(sp^3)(B)(Si) derivatives have been accessed *via* the metal-free insertion of diazo species into B-Si σ-bonds. Such reactivity was first observed by Buynak and Geng in 1995,[3] and is initiated by the interaction of ethyl diazoacetate with the empty *3p* orbital of the B atom in Me$_2$PhSi-Bcat (Bcat= catecholboryl moiety) leading to an 'ate' complex. More recently, Wang and co-workers have revisited the subject providing the synthesis of 1-silyl-1-boryl compounds *via* reaction between the corresponding *N*-tosylhydrazone-derived diazo species and Me$_2$PhSi-Bpin (Bpin= pinacolboryl moiety).[4] 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.[5]

Several interesting *gem*-silylborylations have been developed by reaction of vinylic *gem*-dihalides with Me$_2$PhSi-Bpin in the presence of lithiated bases (Scheme 1a). This methodology, developed by Hiyama and Shimizu, affords 1-boryl-1-silylallenes,[6] and 1-boryl-1-sylilalkenes.[7] The latter example is of fundamental interest, since the access to *gem*-difunctionalization of alkenes represents a direct method towards polysubstituted olefins through stereodivergent approaches. In that context, and considering our ongoing research based on metal-free insertions of diazo synthons into sigma non-symmetric B-B[8] and B-S bonds,[9] we report here the straightforward insertion of the commercially available (trimethylsilyl)diazomethane into bis(pinacolato)diboron (B$_2$pin$_2$). The corresponding multisubstituted HC(Bpin)$_2$(SiMe$_3$) insertion product can eventually be deprotonated in the presence of lithiated bases to generate boron and silicon stabilized carbanions, able to add to a carbonyl function (Scheme 1b). Upon such addition, two possible eliminations can take place: the classical Peterson-type Si-O elimination (Scheme 1b, left) to afford a *gem*-diboron product or the B-O elimination to access the *gem*-silaborated structures (Scheme 1b, right). Some previous examples about the feasibility of the stereoselective B-O *syn*-eliminations have been reported by Endo, Shibata and Morken.[10,11] Interestingly, the Si-O elimination was not observed under our reaction conditions.



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

The synthesis of H-C(Bpin)$_2$(SiMe$_3$) (**1**) can be efficiently completed on gram scale simply by mixing B$_2$pin$_2$ and 2 equiv of (trimethylsilyl)diazomethane (2*M* hexane solution) and heating the mixture at 110 ºC for 24h (87%, isolated yield, Scheme 2).[12]



Scheme 2. Direct access to H-C(Bpin)$_2$(SiMe$_3$) (**1**) on gram scale.

We tentatively examined the deprotonation of H-C(Bpin)$_2$(SiMe$_3$) by adding lithium 2,2,6,6-tetramethylpiperidine (LiTMP) to a solution of **1** in THF at 0 ºC, followed by addition of cyclohexanone 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). This result confirms that B-O elimination is faster than the analogous Si-O Peterson-type reactivity, as it was expected. 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

[a] Mr Enrico La Cascia, Dr. Ana B. Cuenca, Dr. Elena Fernández
Department Química Física i Inorgànica
University Rovira i Virgili
C/Marcel·lí Domingo s/n, Tarragona, Spain
E-mail: mariaelena.fernandez@urv.cat; anabelen.cuenca@urv.cat

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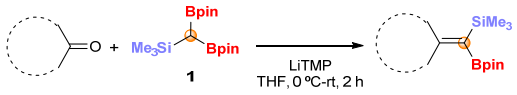
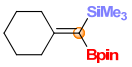
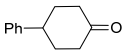
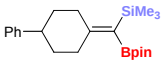
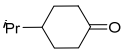
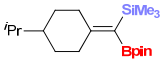
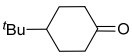
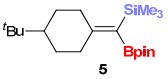
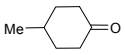
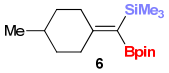
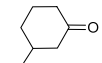
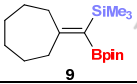
formation of the *gem*-silylborylated product **7** took place (Table 2, entry 7), albeit as a 45:55 mixture of the two possible stereoisomers. Interestingly, 2-methylcyclohexanone lead to the *gem*-dimetalated products **8/8'** in 70% isolated yield and a synthetically useful 30:70 stereoisomeric ratio (Table 1, entry 8) in favor of the isomer **8'** that presents the $SiMe_3$ fragment close to Me at the 2-position. 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]

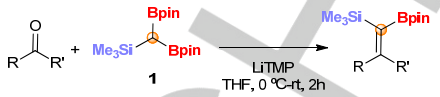


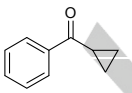
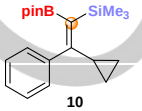
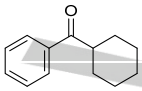
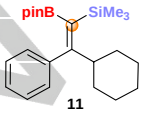
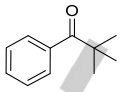
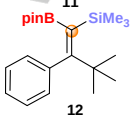
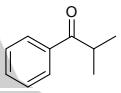
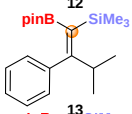
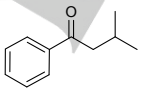
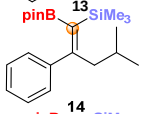
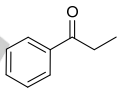
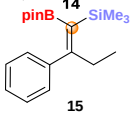
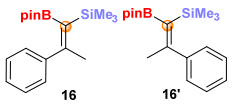
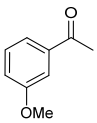
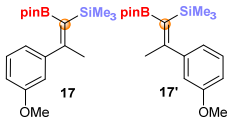
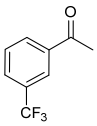
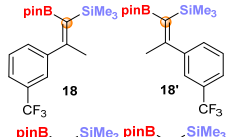
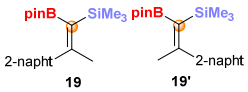
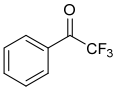
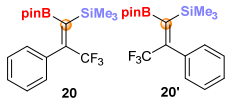
Entry	Substrate	Product	NMR yield (%)[b]	Isolated yields[%] (X/X')[c]
1		 **2**	97	95
2		 **3**	85	83
3		 **4**	89	87
4		 **5**	84	82
5 6[d]		 **6**	95 60	88 55
7		 **7** **7'**	95	90(45/55)
8		 **8** **8'**	75	70(30/70)
9		 **9**	60	56

[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 2 h [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. The cyclopropyl(phenyl)methanone was easily converted to the corresponding *gem*-silylboronate product either with **1** or with the ketone as limiting reagents (Table 2, entries 1,2). Interestingly, the reaction takes place with high degree of stereocontrol (**10**/**10'** = 95/5) as confirmed by NOESY 1D NMR experiments and X-ray diffraction, with the major isomer placing the Bpin moiety *cis* to the Ph group. The reasons for such stereoselectivity might point out an unfavorable steric interaction between the aliphatic substituent on the ketone and a hindered Bpin moiety in the olefination transition state. A plausible interaction between the Ph group and the empty p-orbital on B might contribute to the high stereoselectivity

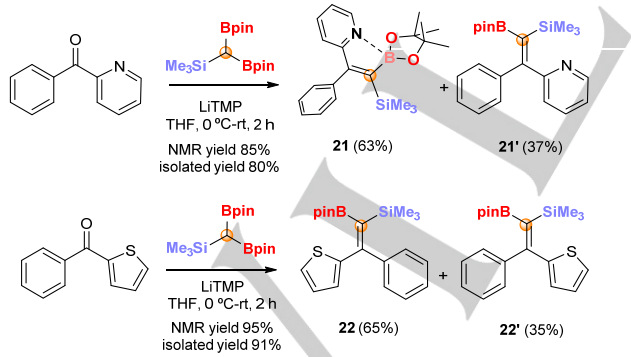
Table 2. *Gem*-silylborylation of non-cyclic ketones with **1**. [a]



Entry	Substrate	Products	NMR yield (%)[b]	Isolated yields[%] (X/X')[c]
1 2[d]		 **10**	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**	62	60(91/9)
7		 **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)

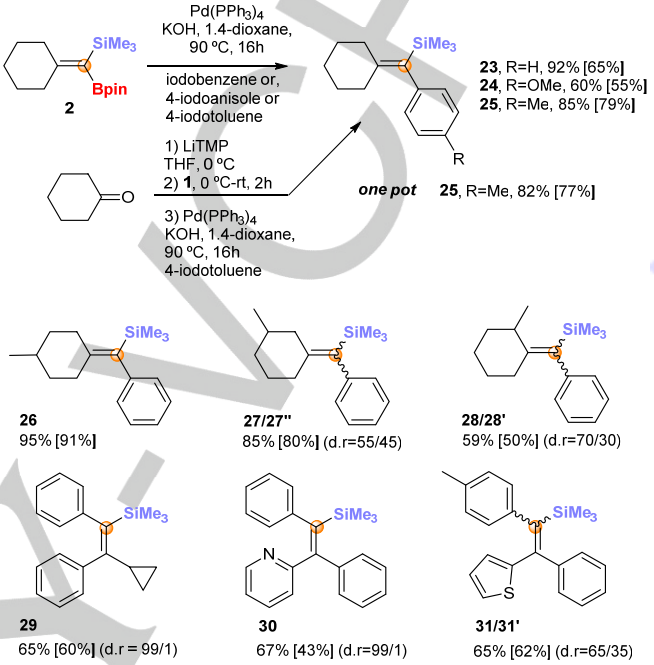
[a] Reaction conditions: **1** (1.2 equiv), ketone, (1.0 equiv, 0.1 mmol), LiTMP (1.4 eq), THF (0.2 mL), from 0 ºC to rt for 2 h [b] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with naphthalene as an internal standard, which was added after the reaction. [c] X/X' diastereoisomeric ratio. [d] **1** (1.0 equiv), ketone, (1.5 equiv), LiTMP (1.2 equiv). [e] 2-napth = 2-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, whose corresponding products **11**, **12** and **13** were obtained in diastereoisomeric ratios up to 99/1 (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 diastereoisomeric ratio slightly decreased to 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 diastereoisomeric ratios about (**X/X'** = 87-90/13-10) in 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 diastereoisomeric ratio lowered to 63/37, (Table 2, entry 12). When diaryl ketone-derived phenyl(pyridin-2-yl)methanone was transformed into the *gem*-silylborated products **21/21'**, the isomeric ratio obtained was 63/37. In this case the major isomer **21** presents the 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 pyridine nitrogen and the 3*p* empty orbital of Bpin that results in a more polar compound (Scheme 3). Compound **21** showed a characteristic ^{11}B NMR signal at 18 ppm, as a consequence of the mentioned B-N interaction. In contrast, the *gem*-silylborylation of phenyl(thiophen-2-yl)methanone provided a mixture of the stereoisomeric silylborylated products **22/22'**, and in that case compound **22** could not be separated from **22'** since the S-B interaction was not observed (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 all-carbon tetrasubstituted olefins. 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 90 ºC during 16 h,[13] as standard reaction conditions. The *gem*-silylboronated product **2** was efficiently transformed into 1-aryl,1-trimethylsilyl-methylenecyclohexane products **23**-**25** (Scheme 4). We also proved that the 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 intermediate *gem*-silylboronate (Scheme 4).

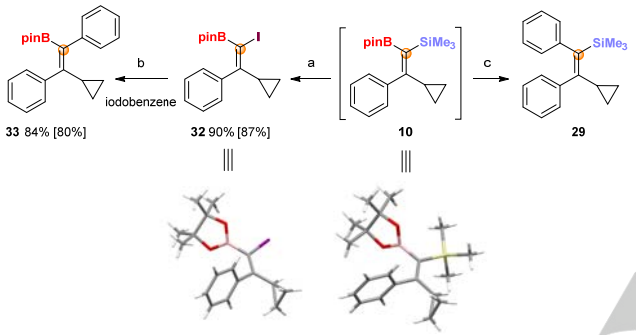


Scheme 4. Cross-coupling of *gem*-silylborylated product **2** and sequential "one pot" *gem*-silylborylation/cross-coupling approach.

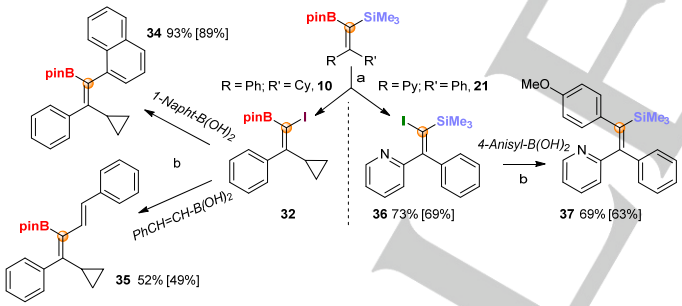
With this convenient approach in our hands, we decided to apply the "*one pot*" protocol to a representative type of cyclic and non-cyclic ketones. The 2-, 3- and 4-methylcyclohexenones, followed the sequence *gem*-silylborylation/cross-coupling reaction providing the corresponding fully substituted vinyl silanes in quantitative yields and moderate diastereoselection (Scheme 4). However, the non-cyclic ketone cyclopropyl(phenyl)methanone was stereoselectively transformed into **29**. We also observed that the B-N interaction in product **21** assisted the selective cross-coupling from the stereoisomeric mixture **21/21'**, since **30** was the exclusive product formed and only traces of **30'** were detected (Scheme 4). In contrast, the *gem*-silylborylation/cross-coupling sequence from phenyl thiophenyl methanone provided a 65/35 mixture of the vinyl silanes **31/31'** (Scheme 4). This methodology complements some of the reported protocols to address the challenging task of all-substituted vinyl silanes synthesis.[7,14]

Alternatively to the cross-coupling of **10** toward 1-silylalkene **29** (Scheme 5), we also focused on the most challenging silicon-based arylation strategy keeping the Bpin unit untouched.[8] To do so, we proceed *via* an attempt to iododesilylate[15] compound **10** using I_2 / $AgNO_3$. Interestingly, product **32**, resulting from the selective halodesilylation of $SiMe_3$ group, was obtained in high yield (Scheme 5). We consider **32** a quite versatile synthetic carbenoid equivalent bearing simultaneously an electrophile and a nucleophile in the same carbon. Compound **32** 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 iododesilylation/cross-coupling in silylboronated products and its usefulness rely in the synthesis and stereoselective control of unusual trisubstituted 1-borylalkenes. Products **34** and **35**, were isolated from the Suzuki-Miyaura cross-coupling reaction of **32** with 1-naphthylboronic acid and *trans*-styrylboronic acid, respectively (Scheme 6). However, attempts 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 6). The cross-coupling reaction of **36** with 4-anisylboronic acid allowed the isolation of trisubstituted vinyl silane **37** with total stereocontrol (Scheme 6).



Scheme 5. Stereochemical course of the sequential cross coupling *via* Suzuki-Miyaura and iododesilylation/cross-coupling of **10**. [a] $AgNO_3$, I_2, 0 ºC, 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 conducted the stereoselective synthesis of all-carbon tetrasubstituted olefins.[16] As a proof of concept, compound **38** was efficiently isolated from the reaction of **33** with 4-iodoanisole in presence of $Pd(PPh_3)_4$. Even the more challenging all-carbon tetrasubstituted alkenes **39** and **40** were also generated from **34** and **35** *via* Pd-catalyzed cross-coupling with 4-iodoanisole and 4-$CF_3C_6H_4I$, respectively (Figure 1). Next, we applied our methodology to the synthesis of (*Z*)-Tamoxifen[14a,17] from the *gem*-silaborated compound **15**. As it can be seen in the Scheme 7, the iododesilylation of **15** afforded compound **41** in 88% isolated yield and in nearly complete stereomeric ratio after purification. The required *trans* Ph group was introduced *via* Suzuki-Miyaura cross-coupling between **41** and iodobenzene to form **42** in 98% yield (95/5; *E*/*Z*). The synthesis is completed by a second cross-coupling that leads to Tamoxifen (≥ 93% *Z*) (**43**) in 65% yield. This modular stereoselective synthesis constitutes one of the most step- and cost-economic routes to this antagonistic prodrug used in all stages of estrogen-receptor-positive breast cancer.[17]

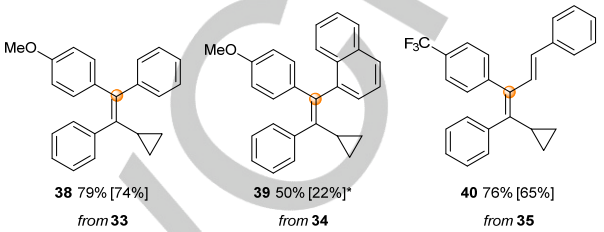
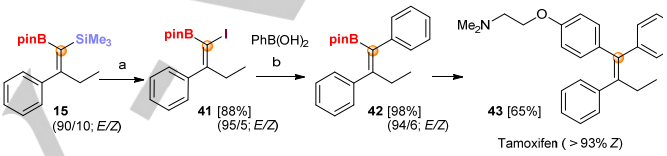


Figure 1. Synthesis of tretrasubstituted alkenes *via gem*-silaborated products. * 85:15 mixture of isomers was isolated after the cross-coupling reaction.



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

We conclude that $HC(Bpin)_2(SiMe_3)$ (**1**) represents a new olefination reagent that can be efficiently prepared *via* insertion of (trimethylsilyl)diazomethane into B_2pin_2. The straightforward access to *gem*-silaborated products opens the door to the modular synthesis of all-carbon tetrasubstituted alkenes *via* silicon or boron-based selective transformations. This novel protocol opens the door to the stereoselective preparation of tetra-substituted olefins, exemplified here by the synthesis of Tamoxifen.

Acknowledgements

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Keywords: olefination reagents • *gem*-silylborated products • insertion • iododesilylation • all-carbon tetrasubstituted alkenes • tamoxifen

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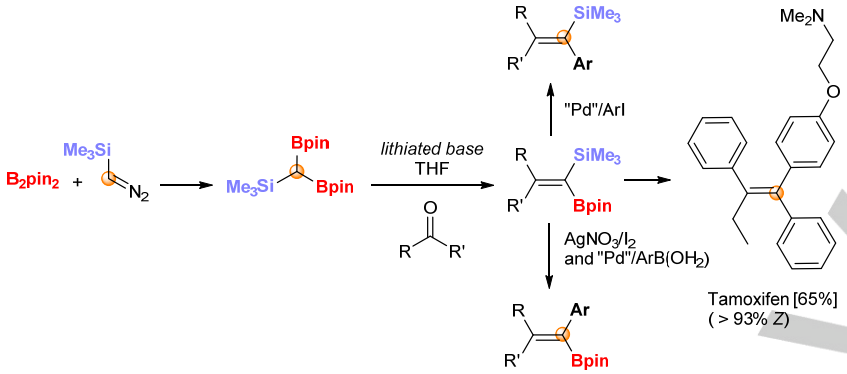

Enrico La Cascia, Ana B. Cuenca*,

Elena Fernández*

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Opportune *gem*-silylborylation of carbonyl compounds: a modular and stereocontrolled entry to tetrasubstituted olefins

The stereocontrol on the synthesis of all-carbon tetrasubstituted alkenes can be achieved by the use of *gem*-silaborated structures that perform selective silicon based or boron based cross-coupling strategies. The straightforward access to *gem*-silaborated olefins, from ketones and $HC(Bpin)_2(SiMe_3)$, is based on the strategic B-O olefination outcome. Selective iododesilylation results in a strategic issue to accomplish the target C-Si cross coupling, and opens the door to the stereoselective preparation tetra-substituted olefins, exemplified here by the synthesis of Tamoxifen.