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Transition-metal-free synthesis of vicinal triborated compounds and selective functionalisation of the internal C-B bond

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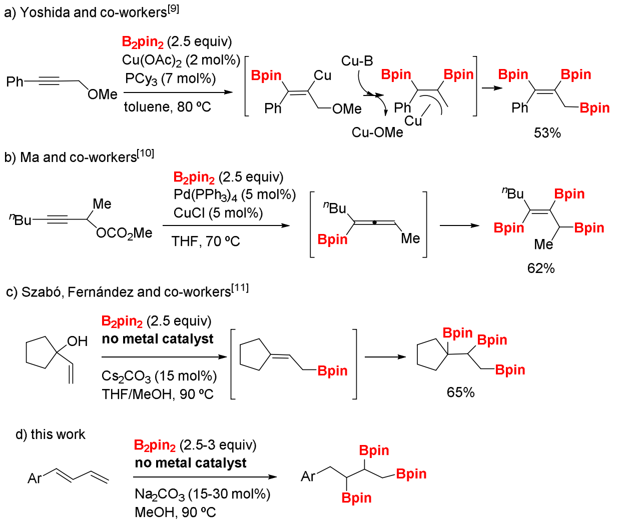
Elliot Davenport,[a,b] Elena Fernandez *[a]

1,2,3-triborated compounds can be prepared by simple nucleophilic borylation of 1,3-dienes, without assistance of metal catalysts. Selective functionalisation of the internal C-B bond of the 1,2,3-triborated compounds, through cross coupling with aryl iodides, highlights the powerful methodology toward polyfunctionalisation.

Triboration reactions have been much less studied than the corresponding hydroboration or diboration reactions, where the addition of H-B or B-B reagents to unsaturated substrates principally provides mono- and diborated products.[1] However, access to triborated compounds significantly enhances the possibilities towards polyfunctionalisation, especially when stereoselectivity is being achieved. That is the case of 1,1,2-triborated alkenes,[2-4] that further undergo stereoselective polyfunctionalization to tetrasubstituted alkenes by consecutive cross-coupling reactions. Similarly, 1,1,1-triborylalkanes,[5-8] have been efficiently prepared towards selective functionalisation.

Introducing three vicinal boryl moieties in a one-pot protocol, represents a challenging reaction. The triboration of alkyne towards 1,2,3-triborated compounds has been accomplished by Yoshida and co-workers[9] via Cu-PCy$_3$ catalysed borylcupration of phenyl 2-alkynyl methyl ether followed by σ-bond metathesis of the π-allyl copper intermediates (Scheme 1a). Alternatively, Ma and co-workers[10] proved a highly selective 1,2,3-triboration of propargylic carbonates to generate (*E*)-propen-1,2,3-triboronates, by using two catalytic systems Pd(PPh$_3$)$_4$ and CuCl, and suggesting the formation of 1,2-allenyl boronate intermediates (Scheme 1b). All the efforts devoted to introduce three C-B bonds in a one-pot sequential reaction required transition metal complexes to activate the borane reagent and facilitate the addition to the saturated or unsaturated substrates. Our group was the first to observe the possibility to conduct a 1,2,3-triboration reaction in a transition-metal-free scenario, using allylic alcohols as substrates and conducting a one-pot allylic borylation/diboration sequence (Scheme 1c).[11] The activation of the B$_2$pin$_2$ reagent was accomplished by the alkoxide formed from MeOH and base, that generates the Lewis acid–base adduct, [Hbase]$^+$[MeO-B$_2$pin$_2$]$^-$ characteristic of a nucleophilic sp^2 boryl unit[12] to promote the tandem performance (Scheme 1c). Since transition-metal-free borylations are gaining a representative space in the field of C-B bond formation,[13] we explored here a new synthetic approach towards 1,2,3-triborated products by the simple addition of B$_2$pin$_2$ and MeOH/base to 1,3-dienes (Scheme 1d)



Scheme 1. Synthetic approaches towards 1,2,3-triborated compounds: a) Cu(II) catalyzed triboration of phenyl 2-alkynyl methyl ether, b) Pd(0)/Cu(I) co-catalyzed triboration of propargyl carbonates, c) transition metal-free triboration of allylic alcohols and d) alternative transition-metal-free triboration in this work

Initial substrate evaluation was conducted with *trans*-1-phenyl-1,3-butadiene (**1**) and 1.1 equiv of B$_2$pin$_2$ in the presence of 15 mol% of Na$_2$CO$_3$ and MeOH as solvent (1 mL).

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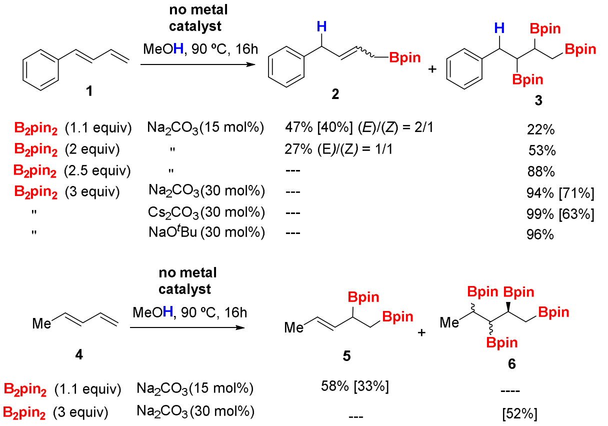
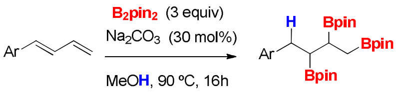
The model reaction was carried out at 90°C and the analysis of the unpurified reaction mixture, by ^{1}H NMR spectroscopy, established 47% conversion towards the 1,4-hydroborated product **2** and 22% of triborated product **3** (Scheme 2). The purification of the allylboronate product **2** allowed its isolation in 40% with a (*E*)/(*Z*) ratio of 2/1, respectively. Remarkably, this is the first attempt to borylate 1,3-dienes in a transition-metal-free context and the results seems to be complementary to Huang and co-workers' work,[14] where the same substrate **1** underwent 1,4-hydroboration with HBpin in the presence of iminopyridine Fe complexes, but forming principally the secondary (*Z*)-allylboronate. The synthesis of primary (*Z*)-allylboronates from the 1,4-hydroboration of **1** has been carried out with Ni catalysts and HBpin[15] or Cu catalysts and B_2pin_2.[16] Under our transition-metal-free initial conditions, we explored the influence of the amount of B_2pin_2, as well as the base involved, and we found that by increasing the amount of diboron reagent to 3 equivalents, the triborated product **3** could be formed exclusively, probably due to the *in situ* transition-metal-free diboration of **2** towards **3** (Scheme 2). Despite the fact that other bases (Cs_2CO_3, NaO^{t}Bu) worked similarly, we selected Na_2CO_3 to extend the study to other 1-substituted 1,3-dienes. When *trans*-1-methyl-1,3-butadiene (**4**) reacted with 1.1 equiv of B_2pin_2 the 1,2-diboration of the terminal alkene took place instead, to form product **5** in 58% NMR yield, (33% isolated) (Scheme 2). However, the excess of B_2pin_2 favored the quantitative formation of 1,2,3,4-tetraborylated product **6**, that could be isolated in 52% yield (Scheme 2). It seems that the competitive 1,2-diboration versus 1,4-hydroboration is favored when there is no conjugation with the alkyl group,[17,18] in contrast to the Fe-Mg catalyzed 1,4-hydroboration of 1-alkyl-substituted 1,3-dienes or 2-alkyl-substituted 1,3-dienes, observed by the groups of Huang and Ritter, respectively.[14,19]

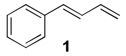
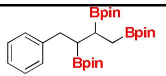
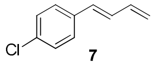
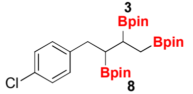
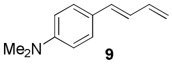
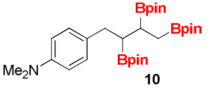
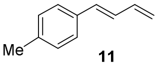
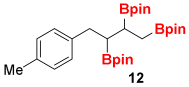
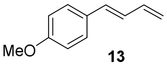
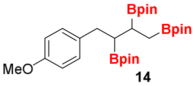
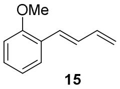
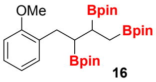
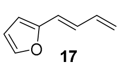
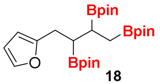
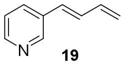
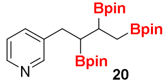


Scheme 2. Transition-metal-free borylation of *trans*-1-phenyl-1,3-butadiene and *trans*-1-methyl-1,3-butadiene.

Based on the optimised reaction conditions for the triboration of *trans*-1-phenyl 1,3-dienes with the Lewis acid–base adduct, $[Hbase]^+[MeO\text{-}B_2pin_2]^-$, we extended the study to a representative scope of *trans*-1-aryl-1,3-butadienes. Table 1 shows the range of aryl substituents that efficiently followed the sequential one-pot 1,4-hydroboration/diboration reaction, with exclusive formation of the 1,2,3-triborated product. The substrate (*E*)-1-(buta-1,3-dien-1-yl)-4-chlorobenzene (**7**) was quantitatively transformed into the corresponding triborated product **8** (Table 1, entry 2), whereas the electron rich substrates (*E*)-4-(buta-1,3-dien-1-yl)-N,N-dimethylaniline (**9**), (*E*)-1-(buta-1,3-dien-1-yl)-4-methylbenzene (**11**) and (*E*)-1-(buta-1,3-dien-1-yl)-4-methoxybenzene (**13**) generated the triborated products **10**, **12** and **14** in 80-99% NMR yield (Table 1, entries 3-5). For the *ortho*-substituted-aryl-1,3-diene (*E*)-1-(buta-1,3-dien-1-yl)-2-methoxybenzene (**15**) the triboration reaction also proceed with high conversions (Table 1, entry 6). Substrates with furyl and pyridyl groups such as (*E*)-2-(buta-1,3-dien-1-yl)furan (**17**) and (*E*)-3-(buta-1,3-dien-1-yl)pyridine (**19**) could be moderately triborated (Table 1, entries 7, 8), although substrate **19** experimented some polymerization as a secondary reaction. Interestingly, two distinctive type of signals appeared in the ^{11}B NMR spectra of triborated products **18** (33.5 and 30.4 ppm) and **20** (34.4 and 22.2 ppm), that might suggest a plausible interaction between the closest Bpin unit and O or n, respectively.

Table 1. Transition-metal-free triboration of *trans*-1-aryl-1,3-butadienes, (*E*)-2-(buta-1,3-dien-1-yl)furan and (*E*)-3-(buta-1,3-dien-1-yl)pyridine.[a]



Entry	Substrate	Product	%NMR Yield[b] [%IY][c]
1	 1	 3	94%[71%]
2	 7	 8	99%[50%]
3	 9	 10	83%[60%]
4	 11	 12	85%[65%]
5	 13	 14	99%[60%]
6	 15	 16	99%[65%]
7	 17	 18	70%[64%]
8	 19	 20	33%[10%]

[a] Reaction conditions: Substrate (0.2 mmol), B_2pin_2 (3 eq), Na_2CO_3 (30 mol%), MeOH (1 mL), 90ºC, 16h. [b] % NMR yields calculated in ^{1}H NMR spectra with naphthalene as internal standard. [c] [% Isolated yields].

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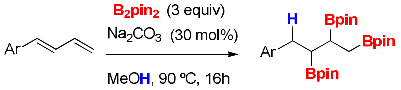
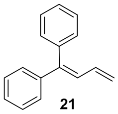
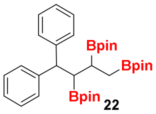
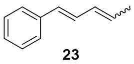
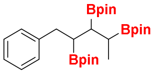
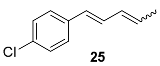
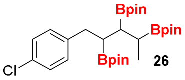
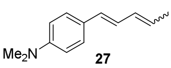
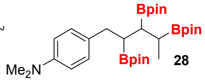
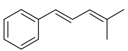
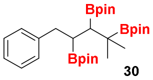
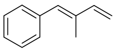
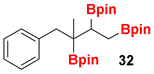
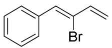
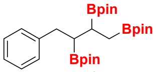
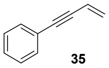
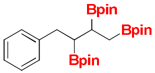
The more sterically hindered substrate buta-1,3-diene-1,1-diyldibenzene (**21**) was triborated under the previous optimized reaction conditions. The expected 1,2,3-triborated product was formed in 56% but the ^{1}H NMR of the crude also showed the presence of 1,4-hydroborated (14%) and 1,2-hydroborated (15%) as byproducts (Table 2, entry 1). The more sterically hindrance in **21** might difficult the diboration from the 1,4-hydroborated intermediate. The internal 1,3-dienes (penta-1,3-dien-1-yl)benzene (**23**), 1-chloro-4-(penta-1,3-dien-1-yl)benzene (**25**) and N,N-dimethyl-4-(penta-1,3-dien-1-yl)aniline (**27**) are triborated with less extension (substrate is still remained in the ^{1}H NMR of the crude) since the first nucleophilic borylation is sterically disfavored (Table 2, entries 2-4). From the previous results we expected no triboration of substrate (*E*)-(4-methylpenta-1,3-dien-1-yl)benzene (**29**), and in fact less than 10% was detected by ^{1}H NMR (Table 2, entry 5).

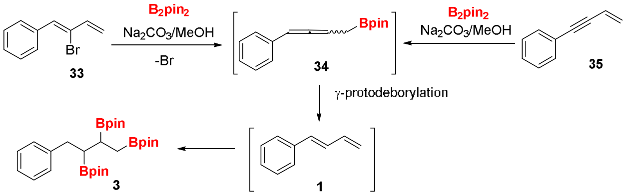
Table 2. Transition-metal-free triboration of sterically hindered *trans*-1-aryl-1,3-butadienes[a]



Entry	Substrate	Product	%NMRYield[%IY][b]
1	 **21**	 **22**	56%[47%]
2	 **23**	 **24**	53%[30%]
3	 **25**	 **26**	40%[20%]
4	 **27**	 **28**	52%[30%]
5[c]	 **29**	 **30**	< 10%
6	 **31**	 **32**	68%[48%]
7	 **33**	 **3**	30%[15%]
8	 **35**	 **3**	34%[31%]

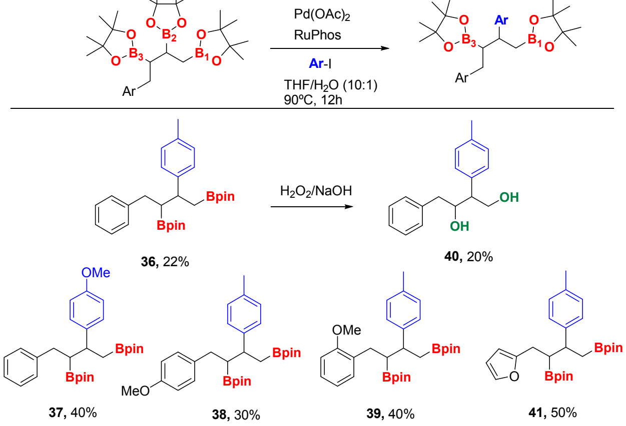
[a] Reaction conditions: Substrate (0.2 mmol), B_2pin_2 (3 eq) Na_2CO_3 (30 mol%), MeOH (1 mL), 90ºC, 16h; [b] %NMR yields, [%Isolated yields]; [c] 110ºC

Interestingly, substrate (*E*)-(2-methylbuta-1,3-dien-1-yl)benzene (**31**) could be efficiently converted to the desired product **32**, despite the methyl-substitution at the internal double bond (Table 2, entry 6). When the similar substrate (*Z*)-(2-bromobuta-1,3-dien-1-yl)benzene (**33**) was borylated, we observed as the unique product the triborated compound **3** (Table 2, entry 7). Its formation might be explained by the bromide elimination after the initial C-B formation, generating an allene intermediate (**34**) that could suffer γ-protodeborylation to form the model 1,3-diene **1** that is *in situ* triborated towards **3** (Scheme 3). In order to confirm the implication of the allene intermediate **34** in the reaction,[20] we conducted the triboration of but-3-en-1-yn-1-ylbenzene (**35**) under the same reaction conditions (Scheme 3). This experiment allowed product **3** as the unique triborated product with similar percentage as the triboration of **33** (Table 2, entry 8). The low yield might be due to the consumption of the diboron reagent along the sequential hydroboration of the original substrate, followed by hydroboration/diboration of the 1,3-diene intermediate



Scheme 3. Transition-metal-free triboration of substrate (*Z*)-(2-bromobuta-1,3-dien-1-yl)benzene and but-3-en-1-yn-1-ylbenzene

In order to explore a plausible polifunctionalisation of the 1,2,3-triborated products, we conducted a straightforward cross coupling reaction of the model triborated product **3** with 1-iodo-4-methylbenzene and, to our delight, we could observe that the internal C-B_2 bond from the 1,2,3-vicinal triborated specie reacted selectively to form the new C-C bond providing the compound **36** (Scheme 4). Similarly, **3** was transformed into the arylated product **37** when reacted with 1-iodo-4-methoxybenzene (Scheme 4). To the best of our knowledge, this is the first time that this type of 1,3-diborated products have been prepared, and only the unsaturated version 2,4-diphenyl 1,3-bis(4,4,5,5-tetramethyl[1,3,2] dioxaborolan-2-yl)-buta-1*Z*,3*E*-diene was prepared through zirconocene-mediated reductive cyclization of alkynylboronates followed by treatment with acid.[21]



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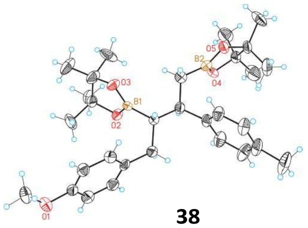
Scheme 4. Cross-coupling of 1,2,3-triborated products with 1-iodo-4-methylbenzene and 1-iodo-4-methoxybenzene in the presence of Pd(OAc)$_2$/RuPhos, and in situ oxidation of **36**.

Unlike to the functionalisation of the terminal C-B bond in 1,2-diborated vicinal products observed by Morken et al.,[22] in our hands the 1,2,3-triborated species allows a selective cross-coupling at the internal B$_2$, under the same reaction conditions. The reaction has been extended to the cross-coupling between 1-iodo-4-methylbenzene and the 1,2,3-triborated compounds **14**, **16** and **18** making the protocol general for *para*- and *ortho*- substituted aryl systems as well as the furyl group forming the desired products **38** , **39** and **41** respectively (Scheme 4). Product **38** could be full characterised by X-Ray diffraction (Figure 1). Following with the attempt to fully functionalise the triborated compounds, we proceeded towards the *in situ* oxidation of the diborated product **36**, in the presence of H$_2$O$_2$/NaOH, forming the corresponding 1,3-butanediol 2,4-diaryl system **40** (Scheme 4).



38

Figure 1. X-Ray Diffraction Data for compound **38**.

In conclusion, we have been able to perform a direct 1,2,3-triboration reaction in a transition metal-free context, by 1,4-hydroboration of 1,3-dienes followed by in situ diboration reaction of the internal double bond. In order to confirm the suggested mechanism, the 1,4-hydroborated intermediate **2** was isolated and a consequent diboration under the same reaction conditions took place to form exclusively product **3**. The reactions are carried out with quantitative conversion for terminal 1,2-dienes, and moderate yields for internal 1,3-dienes, with tolerance to heterofunctional groups. When the 1,2,3-triborated compounds were exposed to cross coupling conditions, only the internal C-B bond could be arylated in a selective way, as a plausible double assistance of the two vicinal boryl moieties. This is an unprecented access to 1,2,3-triborated compounds but also the fact that they can be exclusively functionalised makes this methodology of great applicability in synthetic organic purposes.

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