



## Microwave-assisted one-pot diboration/Suzuki cross-couplings. A rapid route to tetrasubstituted alkenes

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### ABSTRACT

Internal and terminal alkynes undergo rapid platinum(0)-catalyzed diboration with bis(pinacolato)diboron in dioxane to yield *cis*-1,2-bis(boryl)alkenes under sealed vessel microwave conditions. Subsequent addition of aryl bromides, base and a palladium catalyst to the reaction vial followed by resubjection to microwave conditions provides tetrasubstituted ethylenes in high yields via Suzuki cross-coupling of the boron intermediates.

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Transition metal-catalyzed alkene and alkyne boration reactions are attractive methods to produce alkyl- or alkenylboron derivatives with defined regio- and stereochemistry.<sup>1</sup> Organoboron molecules are very useful reagents in organic synthesis, since the carbon–boron bond can be cleaved in a variety of ways leading to a wide range of different functional groups and interesting substrates.<sup>1,2</sup> During the past decades, considerable efforts have been made to develop synthetic routes for the efficient preparation of vicinal *sp*<sup>2</sup> organodiboron derivatives.<sup>3–11</sup> In 1993, Suzuki and Miyaura reported the first addition of tetraalkoxydiboron reagents to terminal and internal alkynes in the presence of a Pt(0) catalyst, resulting in the formation of isomerically pure *cis*-1,2-bis(boryl)alkenes.<sup>3</sup> This diboration reaction is typically performed using bis(pinacolato)diboron (B<sub>2</sub>pin<sub>2</sub>) as a reagent in the presence of 3 mol % of Pt(PPh<sub>3</sub>)<sub>4</sub> catalyst and involves heating of the reaction mixture to 80 °C for 24 h in anhydrous DMF under inert atmosphere (cf. Table 1). Subsequent research has demonstrated that the use of more elaborate bis- or monophosphine<sup>4–6</sup> or phosphine-free<sup>7,8</sup> Pt(0)-based catalysts can often reduce the generally required long reaction times and in some cases allows these diborations to be performed also at lower temperatures, using less polar solvents. In many instances, however, these methods are restricted to the use of more active diboron reagents such as bis(catecholato)diboron.<sup>4,7,8</sup> The first heterogeneous Pt and Pd-catalyzed diboration of alkynes using<sup>2</sup> borametalloarenes

as diboron precursors has recently been described,<sup>9</sup> and some examples for the use of Co(0)<sup>10</sup> and Cu(I)<sup>11</sup> complexes as efficient catalysts in diboration processes were also reported.

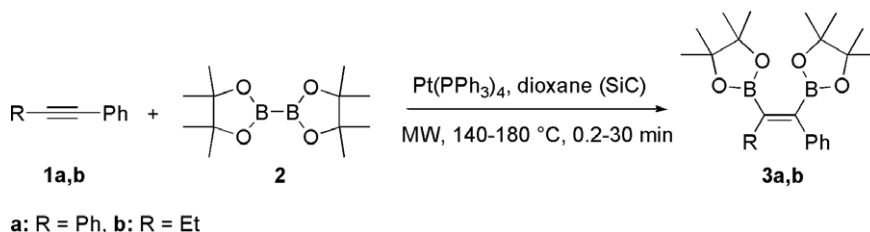
Notwithstanding these advances in transition metal-catalyzed alkyne diboration chemistry,<sup>4–11</sup> there is still need for improvement since most of the more recently published methods apply commercially unavailable catalysts or expensive boron reagents, and have limited substrate scope. On the other hand, the resulting *cis*-1,2-bis(boryl)alkenes **3** have been shown to be valuable starting materials for the preparation of, for example, densely substituted alkenes (such as the anticancer drug tamoxifen),<sup>12</sup> chiral 2,2'-bis-bipyridines,<sup>13</sup> and tetrathiothiophenes<sup>7</sup> helicenes as novel push-pull systems.<sup>14</sup> In this Letter, we describe the rapid generation of *cis*-1,2-bis(boryl)alkenes **3** and their application for the construction of tetrasubstituted alkene derivatives **6**, utilizing a microwave-assisted one-pot diboration/Suzuki cross-coupling reaction sequence that builds on the original Suzuki–Miyaura protocol,<sup>3</sup> involving commercially available Pt(PPh<sub>3</sub>)<sub>4</sub> catalyst/bis(pinacolato)diboron reagent.

As a starting point for our investigation, we examined the diboration of diphenylacetylene (**1a**) with bis(pinacolato)diboron (**2**), using commercially available Pt(PPh<sub>3</sub>)<sub>4</sub> as the catalyst system (Table 1). All initial studies were performed applying controlled single-mode microwave heating in sealed vessels.<sup>15</sup> Screening of reaction conditions for the diboration process focused on the choice of solvent, different amounts of the Pt catalyst, and variations in reaction time and temperature. It was observed that in general the diboration proceeded well in a variety of different

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**Table 1**  
Effect of Pt catalyst concentration on the rate of the diboration reaction of alkynes **1** with bis(pinacolato)diboron (**2**)<sup>a</sup>



Entry	Pt(PPh <sub>3</sub> ) <sub>4</sub> (mol %)	Temperature (°C)	<b>1a</b> time (min) <sup>b</sup>	<b>1a</b> TOF (h <sup>-1</sup> )	<b>1b</b> time (min) <sup>b</sup>	<b>1b</b> TOF (h <sup>-1</sup> )
1	3	140	20	100	2	1000
2	3	180	5	400	0.2	12,000
3	1	180	20	300	0.5	12,000
4	0.1	180	30	2000	1	60,000
5	0.05	180	—	—	7	17,200

<sup>a</sup> Reaction conditions: single-mode microwave irradiation (Biotage Initiator 8 EXP 2.0, 400 W), 5 mL sealed Pyrex microwave vial, 0.3 mmol alkyne **1**, 1.1 equiv bis(pinacolato)diboron (**2**), 0.05–3 mol % Pt(PPh<sub>3</sub>)<sub>4</sub>, 480 μL dioxane, magnetic stirring, ca. 1 g SiC passive heating element, external IR temperature monitoring.

<sup>b</sup> Reaction time (fixed hold time) required for full conversion (GC–MS) at the maximum set temperature (ramp time ca. 1 min).

solvents such as MeCN, dioxane, THF or DME. The use of the originally applied<sup>3</sup> DMF as solvent for our microwave-heated process was not considered due to the known instability of DMF at the high reaction temperatures typically used in sealed-vessel microwave chemistry.<sup>15</sup> Taking into account the second reaction step in our anticipated one-pot diboration/Suzuki protocol, dioxane and MeCN were selected as solvents of choice for subsequent optimization.

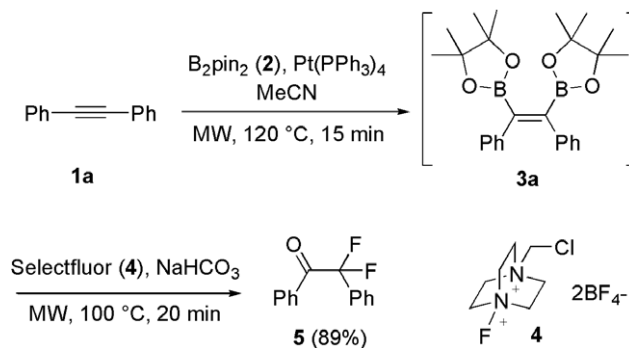
The distinct effect of catalyst concentration and reaction temperature on the rate of diboration is highlighted in Table 1. For diphenylacetylene (**1a**), for example, the catalyst-loading can be reduced from the originally used 3 mol % to 0.1 mol %. While this transformation was reported by Suzuki and Miyaura to require 24 h at 80 °C using 3 mol % of Pt(PPh<sub>3</sub>)<sub>4</sub> catalyst,<sup>3</sup> we find that using sealed-vessel microwave heating the same diboration can be completed in 20 min at 140 °C or in 5 min at 180 °C. This corresponds to a significant increase in catalyst turnover frequency (TOF) from 1.7 h<sup>-1</sup> to 400 h<sup>-1</sup>. Reducing the amount of catalyst from 3 mol % to 0.1 mol % the diboration requires 30 min for completion with a further increase in catalyst efficiency (TOF 2000 h<sup>-1</sup>). For the more reactive 1-phenyl-2-butyne starting material **1b**,<sup>12</sup> full conversion to *cis*-1,2-bis(boryl)alkene **3b** can be achieved with only 0.05 mol % of the Pt catalyst at 180 °C in 7 min (entry 5). Applying the more typically used 3 mol % catalyst loading the diboration can be completed within 10 s at 180 °C. Previous diboration studies applying conventional heating at 80 °C have reported reaction times around 24 h for 1-phenyl-2-butyne (**1b**).<sup>3,12</sup>

Both diborations are very clean without any indication of byproduct formation. Conversions can easily be monitored by GC–MS and the purity/identity of the resulting *cis*-1,2-bis(boryl)alkenes **3** was further established by <sup>1</sup>H NMR spectroscopy. We have found that using a sealed microwave vial diborations of this type can be performed without inert gas atmosphere in nondegassed commercially available dioxane. One of the best sets of conditions for the diboration of both internal alkyne substrates **1a,b** utilized 1.1 equiv of bis(pinacolato)diboron (**2**), 0.1 mol % of Pt(PPh<sub>3</sub>)<sub>4</sub> as a catalyst at 180 °C (5–6 bar) for 30 min (for **1a**) or 1 min (for **1b**) in dioxane using controlled microwave heating. Since dioxane is a virtually microwave transparent solvent,<sup>15</sup> the use of a silicon carbide-passive heating element was required in order to achieve reaction temperatures >120 °C.<sup>16</sup> While the observed rapid transition metal-catalyzed diborations are impressive, it should be emphasized that the increase in reaction rate on going from conventional heating to microwave heating is probably the consequence of a purely thermal effect as confirmed

by a control experiment applying conventional heating in a sealed reaction vessel at a similar internal reaction temperature (for further information, see the [Supplementary data](#)).

With optimized conditions for rapid alkyne diborations in hand, the usefulness of this efficient entry to *cis*-1,2-bis(boryl)alkenes was demonstrated by electrophilic fluoro-deboration of the resulting bis(boryl)alkene **3a**, using Selectfluor (**4**) as reagent according to our recently published procedure (Scheme 1).<sup>17</sup> While fluorination of **3a** leading to  $\alpha,\alpha$ -difluorinated carbonyl compound **5** under conventional conditions required 15 h at room temperature for completion,<sup>17</sup> the high-temperature microwave protocol was considerably faster. Using MeCN as solvent, the diboration of diphenylacetylene (**1a**) using 1.1 equiv of bis(pinacolato)diboron reagent (**2**) and 3.0 mol % of Pt(PPh<sub>3</sub>)<sub>4</sub> catalyst progressed to full conversion after 15 min at 120 °C. In a subsequent reaction step, 3.0 equiv of Selectfluor (**4**) and 2.5 equiv of NaHCO<sub>3</sub> were added into the microwave reaction vial. After resealing, the reaction mixture was subjected to microwave-heating for an additional 20 min at 100 °C. After basic workup and column chromatography, the desired 2,2-difluoro-1,2-diphenylethanone **5** was obtained in 89% isolated yield (Scheme 1).<sup>17</sup>

We next focused on the development of a high-speed one-pot diboration/Suzuki cross-coupling protocol. We initially considered the possibility to use a Pt(0) catalyst for both the diboration and the Suzuki cross-coupling step. While Pt-catalyzed cross-coupling reactions of organoboronic acids have been reported in the literature, the general success of Pt catalysts in these transformations is rather limited, as both oxidative addition and reductive elimination are slower as compared to the corresponding Pd complexes.<sup>18</sup>



**Scheme 1.** One-pot diboration/fluorination reaction.

After extensive experimentation involving a variety of different solvent systems, bases, and reaction conditions (see the [Supplementary data](#)) the concept of a unified Pt catalytic system for our diboration/Suzuki cross-coupling protocol had to be abandoned. This was mainly a consequence of the fact that the Suzuki reaction generally requires aqueous basic conditions.<sup>19</sup> Due to the comparatively slow Pt-catalyzed Suzuki cross-coupling, the competing deboration processes could not be prevented.

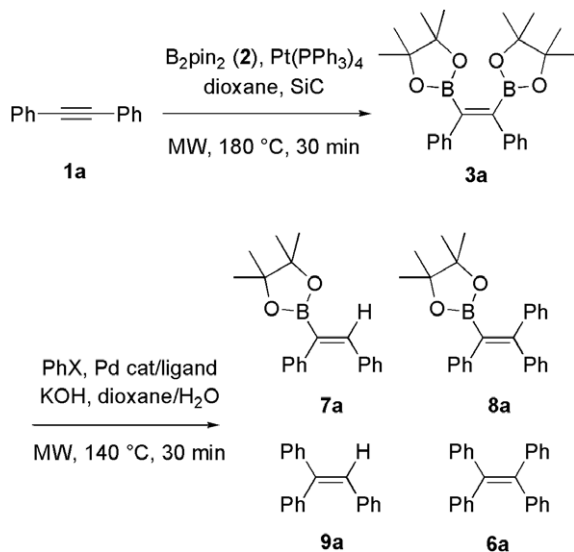
In contrast to the results obtained using a Pt catalyst, the corresponding Pd-catalyzed bis-Suzuki cross-couplings involving *cis*-1,2-bis(boryl)alkenes **3** and aromatic halides<sup>3,12–14</sup> performed very well under microwave conditions ([Table 2](#)). Building on our previous experience, the screening of the reaction conditions for the coupling of bis(pinacol)ester **3a** with aromatic halides was performed by tuning all the main factors: solvent, base, type and concentration of the Pd catalyst, aromatic halide, reaction temperature, and time. Based on the successful use of dioxane in the diboration step ([Table 1](#)), a 3:1 mixture of dioxane/H<sub>2</sub>O was rapidly identified as a very suitable reaction medium for these Suzuki couplings. In conjunction with KOH as a strong base for activation of the diboron reagent, rapid cross-couplings were generally observed. As far as the palladium catalyst is concerned, most of the

traditional catalyst/ligand systems used for Suzuki cross-couplings such as Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd(OAc)<sub>2</sub>, Pd(OAc)<sub>2</sub>/PPh<sub>3</sub>, Pd(OAc)<sub>2</sub>/tributylphosphine, Pd(OAc)<sub>2</sub>/dppf, PdCl<sub>2</sub>(dppf)/dppf, and immobilized Pd sources (Fibrecat 1001) provided useful conversions and high selectivities.<sup>20</sup> For the specific selected examples discussed herein, the use of Pd(PPh<sub>3</sub>)<sub>4</sub> and Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> generally provided optimum results. Catalytic loadings apparently play a very important role in controlling the selectivity between the desired bis-Suzuki cross-coupling product **6a**, the mono-Suzuki coupling product **8a** and the deboration byproducts **7a** and **9a** ([Table 2](#)). For very low catalyst loadings (0.001 mol %), the major product in the reaction of bis(pinacol)ester **3a** with iodobenzene is the deboration byproduct **9a** ([Table 2](#), entry 1), while the use of 0.1 mol % of the same catalyst allows a 93% conversion to the desired cross-coupling product **6a** ([Table 2](#), entry 6). Following reaction optimization of the Suzuki cross-coupling starting from isolated bis(pinacol)ester **3a**, a further fine tuning of the reaction conditions was performed combining both reaction steps, the Pt-catalyzed diboration and the Pd-catalyzed Suzuki cross-coupling in one sequence. Using the crude reaction mixture of bis(pinacol)ester **3a** for the Suzuki coupling step required an increase of the catalytic loading of Pd in comparison to experiments starting from pure bis(pinacol)ester **3a** (compare entries 6 and 7). Ultimately, the reaction proceeded most effectively using 1 mol % of Pd(OAc)<sub>2</sub>, 2 mol % of PPh<sub>3</sub> as ligand, 2 equiv of bromobenzene, and 6 equiv of KOH in dioxane/H<sub>2</sub>O 3:1 as a solvent. Microwave heating at 140 °C for 30 min provided full conversion and 97% HPLC selectivity for the desired product **6a**, leading to a 94% isolated yield of pure product ([Table 2](#), entry 10).<sup>21</sup> In comparison, conventionally processed Suzuki cross-couplings involving bis(pinacol)esters of type **3** and aryl halides require 12 h at 90 °C for completion.<sup>3</sup>

With optimized conditions for a microwave-assisted one-pot diboration/Suzuki cross-coupling protocol in hand, we then focused our attention on the scope and limitations of this protocol and to the generation of a small collection of 1,2-*cis*-substituted alkenes **6** ([Table 3](#)). For this purpose, we selected eight terminal and internal alkynes **1a–h** as starting materials in combination with seven different substituted bromobenzene derivatives. As can be seen from the data presented in [Table 3](#), some minor adjustments in both catalyst loading and reaction time were necessary in the diboration step for the less reactive, aromatic internal alkynes **1d–h** and for terminal alkyne **1h**. Gratifyingly, no changes were required for the Suzuki procedure and in all 12 cases the reaction proceeded to completion within 30 min at 140 °C. In three cases ([Table 3](#), entries 3, 7, and 12) small amounts (<15%) of the corresponding *trans* alkene-isomer was detected by NMR spectroscopy (see [Supplementary data](#)). The constitution of the major *cis*-isomer was confirmed by 2D NMR experiments (NOESY, HMBC). Importantly, all of the utilized alkynes were transformed to the desired final *cis*-alkene derivatives **6** within ca. 0.5–1.5 h overall processing time. The isolated yields after column chromatography were between 21% and 98%.<sup>22</sup>

In conclusion, we have developed a microwave-assisted one-pot diboration/Suzuki cross-coupling protocol that allows the rapid synthesis of tri- and tetrasubstituted ethylenes. Taking advantage of sealed-vessel microwave processing at high temperatures both steps in the sequence were dramatically improved. For the Pt-catalyzed diboration reaction **1**→**3**, reaction times were reduced from 12 h using conventional heating at 80 °C to less than a minute using microwave processing at 180 °C for a selection of seven internal and one terminal alkyne. At the same time, we have shown that the amount of Pt catalyst can be reduced from 3 mol % to 0.1 mol % without loss of efficiency. Combined with the higher reaction rates, this leads to a significant increase in catalyst turnover frequencies. Similarly, in the Pd-catalyzed Suzuki cross-coupling step **3**→**6**, the necessary reaction times of 12 h using

**Table 2**  
Optimization of reaction conditions for the one-pot diboration/Suzuki cross-coupling<sup>a</sup>



Entry	PhX	Catalyst	Catalyst (mol %)	Conv. <sup>b</sup> 7a/8a/9a/6a	Yield <sup>c</sup> (%)
1	PhI	Pd(PPh <sub>3</sub> ) <sub>4</sub>	0.001	22/0/65/13	—
2	PhI	Pd(PPh <sub>3</sub> ) <sub>4</sub>	0.004	3/0/28/69	—
3	PhI	Pd(PPh <sub>3</sub> ) <sub>4</sub>	0.008	0/0/21/79	—
4	PhI	Pd(PPh <sub>3</sub> ) <sub>4</sub>	0.01	0/0/18/81	—
5	PhBr	Pd(PPh <sub>3</sub> ) <sub>4</sub>	0.02	0/0/17/83	—
6	PhBr	Pd(PPh <sub>3</sub> ) <sub>4</sub>	0.1	0/0/7/93	—
7 <sup>d</sup>	PhBr	Pd(PPh <sub>3</sub> ) <sub>4</sub>	0.1	3/7/53/37	—
8 <sup>d</sup>	PhBr	Pd(OAc) <sub>2</sub> /PPh <sub>3</sub>	0.1/0.2	0/0/20/80	56
9 <sup>d</sup>	PhBr	Pd(OAc) <sub>2</sub> /PPh <sub>3</sub>	0.2/0.4	0/0/15/85	72
10 <sup>d</sup>	PhBr	Pd(OAc) <sub>2</sub> /PPh <sub>3</sub>	1/2	0/0/3/97	94

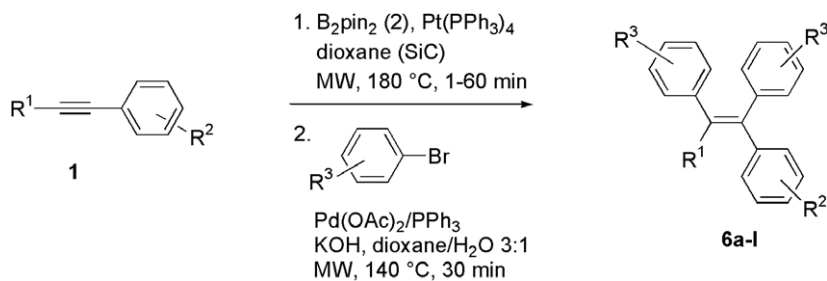
<sup>a</sup> Single-mode microwave irradiation (Biotage Initiator 8 EXP 2.0, 400 W), 5 mL sealed Pyrex microwave vial, magnetic stirring, external IR temperature monitoring. For conditions for step 1 (diboration), see [Table 1](#) entry 4. For step 2 (Suzuki reaction): 2 equiv of PhX, 6 equiv of KOH, 0.001–1 mol % Pd, dioxane/H<sub>2</sub>O 3:1 (600 μL), 140 °C, 30 min. For more details, see Ref. 21.

<sup>b</sup> Product distribution refers to relative peak area (%) ratios of crude HPLC–UV (215 nm) traces.

<sup>c</sup> Isolated product yield after column chromatography.

<sup>d</sup> Data for one-pot diboration/Suzuki cross-coupling method.

**Table 3**  
One-pot diboration/Suzuki cross-coupling of alkynes **1** with arylbromides<sup>a</sup>



Entry	<b>1</b>	R <sup>1</sup>	R <sup>2</sup>	Pt(PPh <sub>3</sub> ) <sub>4</sub> (mol %)	Time <sup>b</sup> (min)	R <sup>3</sup>	Yield <sup>c</sup> (%)
1	<b>1a</b>	Ph	H	0.1	30	H	94
2	<b>1a</b>	Ph	H	0.1	30	<i>m</i> -CN	73
3	<b>1b</b>	Et	H	0.1	1	<i>p</i> -OMe	98
4	<b>1b</b>	Et	H	0.1	1	<i>m</i> -Me	69
5	<b>1b</b>	Et	H	0.1	1	<i>p</i> -CN	93
6	<b>1c</b>	Pr	H	0.1	3	H	73
7	<b>1c</b>	Pr	H	0.1	3	<i>p</i> -OMe	96
8	<b>1d</b>	<i>p</i> -CF <sub>3</sub> Ph	<i>p</i> -OMe	2	60	<i>p</i> -OMe	59
9	<b>1e</b>	<i>p</i> -CF <sub>3</sub> Ph	<i>p</i> -CF <sub>3</sub>	1	60	<i>p</i> -Cl	21
10	<b>1f</b>	Ph	OMe	2	60	<i>p</i> -CHO	66
11	<b>1g</b>	<i>p</i> -OMePh	OMe	1	30	<i>p</i> -CHO	62
12	<b>1h</b>	H	OMe	1	30	H	60

<sup>a</sup> Single-mode microwave irradiation (Biotage Initiator 8 EXP 2.0, 400 W), 5 mL sealed Pyrex microwave vial, magnetic stirring, external IR temperature monitoring. For conditions, for step 1 (diboration), see Table 1, entry 4; for step 2 (Suzuki reaction), see Table 2, entry 10. For more details, see the Supplementary data.

<sup>b</sup> Hold time required for full diboration (GC–MS) at 180 °C (ramp time ca 1 min).

<sup>c</sup> Isolated product yield after column chromatography.

conventional heating at 90 °C were reduced to 30 min at 140 °C using sealed-vessel microwave heating. The combined sequence allows the efficient preparation of densely functionalized ethylenes of the tamoxifen type.

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## Supplementary data

Supplementary data associated with this article (experimental procedures, NMR spectra) can be found in the online version at, doi:10.1016/j.tetlet.2008.06.017.

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- Typical procedure (Table 2, entry 10): A 5 mL microwave process vial was charged with a stir bar and a SiC heating element (ca. 1 g). To the vessel were added bis(pinacolato)diboron **2** (83.8 mg, 0.33 mmol), freshly prepared Pt(PPh<sub>3</sub>)<sub>4</sub> stock solution (100 μL, 0.003 M solution in dioxane, 0.0003 mmol, 0.1 mol %), and diphenylacetylene (**1a**) (53.5 mg, 0.3 mmol). After the addition of dioxane (380 μL) the reaction vessel was sealed and the mixture was subsequently heated in a microwave reactor at 180 °C for 30 min. After cooling

and opening of the sealed vial, bromobenzene (63.2  $\mu$ L, 0.6 mmol), freshly prepared Pd(OAc)<sub>2</sub> stock solution (100  $\mu$ L, 0.03 M solution in dioxane, 1 mol %), freshly prepared PPh<sub>3</sub> stock solution (20  $\mu$ L, 0.3 M solution in dioxane, 2 mol %), and KOH (200  $\mu$ L, 9 M solution in H<sub>2</sub>O) were added and the reaction mixture subsequently heated under sealed vessel microwave conditions at 140 °C for 30 min. After cooling, H<sub>2</sub>O (60 mL) was added and the crude reaction mixture was extracted with CHCl<sub>3</sub> (3  $\times$  20 mL). The combined organic phases were dried over MgSO<sub>4</sub> and the solvent was

removed under reduced pressure. Purification by flash chromatography on silica gel (dichloromethane/hexanes) provided 93.7 mg (94%) of tetraphenylacetylene **6a** as a white solid, mp 226–228 °C.

22. In addition to bis-Suzuki reactions of bis(pinacol)esters **3** with aryl bromides, we have also attempted sequential mono-Suzuki cross-coupling protocols. In agreement with previous reports (Ref. 12), we find these transformations to be rather unselective and to produce mixtures of the corresponding regioisomers (see [Supplementary data for further information](#)).