

## Supplementary Materials

### *Highlights on the general preference for multi- over mono-coupling in the Suzuki-Miyaura reaction*

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## S1. GC analyses

The GC analyses were performed under the following conditions:

- GC Method – initial oven temperature = 100 °C ; initial time = 1 min  
heating rate = 10 °C/min  
final oven temperature = 290 °C ; final time = 10 min  
 $T(\text{injector}) = 290\text{ °C}$ ;  $T(\text{detector}) = 290\text{ °C}$

– Gas flow rates: Air = 235 mL/min, N<sub>2</sub> = 64 mL/min, H<sub>2</sub> = 23 mL/min.

The following reference samples (commercially obtained or previously synthesized) were injected for establishment of compound retention times,  $t_r$  (in min.):

→ biphenyl – 6.2	→ 4,4'-dimethoxy-1,1'-biphenyl – 12.0 *
→ 1,2-dibromobenzene – 4.2	→ 4,4''-dimethoxy-1,1':4,1''-terphenyl – 22.0 *
→ 1,3-dibromobenzene – 3.7	→ 4'-bromo-[1,1'-biphenyl]-4-carbaldehyde – 12.9 *
→ 1,4-dibromobenzene – 3.8	→ [1,1'-biphenyl]-4,4'-dicarbaldehyde – 13.2 *
→ 2-bromobiphenyl – 8.8	→ [1,1':4,1''-terphenyl]-4,4''-dicarbaldehyde – 25.9 *
→ 3-bromobiphenyl – 8.3	→ 1,2,4-tribromobenzene – 7.3
→ 4-bromobiphenyl – 9.9	→ 1,3,5-tribromobenzene – 6.7
→ <i>ortho</i> -terphenyl – 12.5	→ 1,2,4-triphenylbenzene – 19.6
→ <i>meta</i> -terphenyl – 14.8	→ 1,3,5-triphenylbenzene – 21.5
→ <i>para</i> -terphenyl – 15.3	→ 1,1'-dibromoferrocene – 10.9
→ 1-bromo-4-iodobenzene – 5.3	→ 1-phenyl-1'-bromoferrocene – 15.6 *
→ 4-iodobiphenyl – 11.3 *	→ 1,1'-diphenylferrocene – 19.4
→ 1,4-diiodobenzene – 6.8	→ 2,5-dibromothiophene – 3.0
→ 4-methoxy-1,1'-biphenyl – 8.9	→ 2-bromo-5-phenylthiophene – 9.3 *
→ [1,1'-biphenyl]-4-carbaldehyde – 9.6	→ 2,5-diphenylthiophene – 15.1
→ 4-bromo-4'-methoxy-1,1'-biphenyl – 12.3 *	

The compounds marked with an asterisk, \*, were not purchased nor synthesized and thus their retention times were not directly determined by GC. Since they are all mono-coupling intermediates of

the respective Suzuki-Miyaura reactions, their retention times were taken as those corresponding to the peak between the peaks of the non-substituted and bis-coupling products (intermediate retention time). According to the following arguments it is justifiable to ascribe the middle peak to the mono-coupling product: 1) in the other synthesis where all the three products were characterized the middle peak corresponds to the mono-coupling compound; 2) according to what is known for the Suzuki reaction all the three products are expected to form in significant quantities; 3) the mono-coupling compound, due to its intermediate molecular size, most probably has an intermediate affinity for the stationary phase of the GC and intermediate volatility, which will result in an intermediate retention time. For the syntheses with methoxy (–OCH<sub>3</sub>) and formyl (–CHO) derivatives the distinction between the mono-intermediate, Br-Ph-Ph-R, and the homocoupling side-product, R-Ph-Ph-R, was less clear. To distinguish between them, an additional Suzuki coupling was performed on the final mixture (the residue after evaporation of the organic phase) by adding more boronic acid (~0.34 mmol), base (~0.56) mmol, and Pd(OAc)<sub>2</sub> catalyst (~0.04 mmol), in water and DMF. After 2 h, extraction with CH<sub>2</sub>Cl<sub>2</sub> and GC analysis of the new organic phase revealed the peak of the mono-intermediate as the one that decreased in ratio.

The GC calibration was made by calculating a constant, *K*, for each compound that converts the observed peak area, *A* (translated as GC counts), into its molar concentration, *C* (M), in the solution being analyzed, using the equation:  $K = A / C$ . The GC calibration experiments were made by dissolving known masses of the compounds in flasks with CH<sub>2</sub>Cl<sub>2</sub>. The results for the GC calibration are summarized in table S1. The corrected % selectivity of a specified product, *P<sub>i</sub>*, is then calculated from the GC chromatogram according to the equation:

$$\% \text{ selectivity } (P_i) = \frac{F(P_i)}{\sum F(P_i)}$$

where, for each product, *F(P<sub>i</sub>)* defines the quotient:

$$F(P_i) = \frac{A(P_i)}{K(P_i)}$$

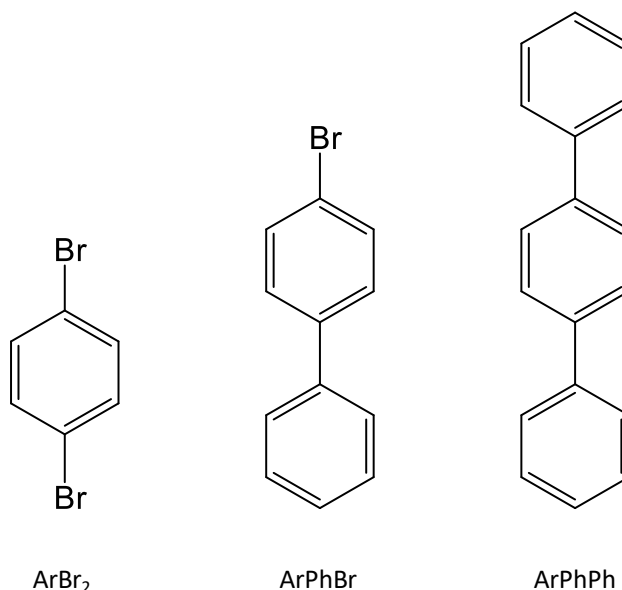
For the cases where several isomers were presented (e.g. *ortho*-, *meta*- and *para*-terphenyl), the GC calibration was done for only one isomer and the same calibration constant was assumed for the other isomers. For the compounds marked with an asterisk \* in table S1, the calibration constant, *K*, was estimated using a group-additivity model that considers the contributions of the halogens and aromatic groups. These calculations were performed using the Solver tool of Microsoft Excel 2016.

**Table S1.** GC calibration results; solvent: CH<sub>2</sub>Cl<sub>2</sub>. The asterisk \* denotes the compounds for which *K* was estimated by a group-additivity method.

Compound	<i>C</i> / mol·dm <sup>-3</sup>	<i>A</i> / counts	<i>K</i> / counts·M <sup>-1</sup>
biphenyl	7.19·10 <sup>-3</sup>	1.53·10 <sup>6</sup>	2.13·10 <sup>8</sup>
1,4-dibromobenzene	4.79·10 <sup>-3</sup>	6.59·10 <sup>5</sup>	1.38·10 <sup>8</sup>
<i>para</i> -terphenyl	5.71·10 <sup>-3</sup>	2.43·10 <sup>6</sup>	4.26·10 <sup>8</sup>
1-bromo-4-iodobenzene	3.76·10 <sup>-3</sup>	4.42·10 <sup>5</sup>	1.18·10 <sup>8</sup>
1,4-diiodobenzene	4.00·10 <sup>-3</sup>	4.15·10 <sup>5</sup>	1.04·10 <sup>8</sup>
4-bromobiphenyl	4.98·10 <sup>-3</sup>	1.40·10 <sup>6</sup>	2.81·10 <sup>8</sup>
1,3,5-tribromobenzene	4.12·10 <sup>-3</sup>	6.96·10 <sup>5</sup>	1.69·10 <sup>8</sup>
1,3,5-triphenylbenzene	3.50·10 <sup>-3</sup>	2.00·10 <sup>6</sup>	5.72·10 <sup>8</sup>
4-methoxy-1,1'-biphenyl	7.30·10 <sup>-3</sup>	1.62·10 <sup>6</sup>	2.22·10 <sup>8</sup>
[1,1'-biphenyl]-4-carbaldehyde	7.33·10 <sup>-3</sup>	1.56·10 <sup>6</sup>	2.13·10 <sup>8</sup>
4-iodobiphenyl *	---	---	2.49·10 <sup>8</sup>
4-bromo-4'-methoxy-1,1'-biphenyl *	---	---	2.05·10 <sup>8</sup>
4,4'-dimethoxy-1,1'-biphenyl *	---	---	2.21·10 <sup>8</sup>
4,4''-dimethoxy-1,1':4,1''-terphenyl *	---	---	3.42·10 <sup>8</sup>
4'-bromo-[1,1'-biphenyl]-4-carbaldehyde *	---	---	1.95·10 <sup>8</sup>
[1,1'-biphenyl]-4,4'-dicarbaldehyde *	---	---	2.02·10 <sup>8</sup>
[1,1':4,1''-terphenyl]-4,4''-dicarbaldehyde *	---	---	3.23·10 <sup>8</sup>
1,1'-dibromoferrocene *	---	---	1.42·10 <sup>8</sup>
1-phenyl-1'-bromoferrocene *	---	---	2.76·10 <sup>8</sup>
1,1'-diphenylferrocene *	---	---	4.10·10 <sup>8</sup>
2,5-dibromothiophene *	---	---	1.42·10 <sup>8</sup>
2-bromo-5-phenylthiophene *	---	---	2.76·10 <sup>8</sup>
2,5-diphenylthiophene *	---	---	4.10·10 <sup>8</sup>

## S2. Statistical analysis of reaction selectivity

The statistical predicted outcome for the Suzuki-Miyaura reactions was calculated considering the following conditions:



1. A 1:1 stoichiometry between the halogenated reagent ( $\text{ArBr}_2$ ) and boronic acid (BA) was considered;
2. Since there are twice the number of coupling positions in  $\text{ArBr}_2$  compared to  $\text{ArPhBr}$ , it follows that, if no additional factors are considered:  $k(\text{ArBr}_2) = 2 \cdot k(\text{ArPhBr})$ , where  $k$  is the rate constant;
3. The analysis was made in a stepwise fashion, considering the reaction stoichiometry;
4. BA was defined as reacting 1 molecule per step;
5. The probability of BA attacking  $\text{ArBr}_2$  and  $\text{ArPhBr}$  was calculated considering the amount of each compound at each step and the condition  $k(\text{ArBr}_2) = 2 \cdot k(\text{ArPhBr})$ ;
6. The quantities of  $\text{ArBr}_2$  and of each product,  $\text{ArPhBr}$  and  $\text{ArPhPh}$ , for each step were calculated according to the relative probabilities of forming and reacting for each species;
7. This analysis was step-iterated until no molecules of BA remained; the final relative proportions of the three different products ( $\text{ArBr}_2$ ,  $\text{ArPhBr}$  and  $\text{ArPhPh}$ ) were taken as the ones corresponding to this last step;
8. The same analysis was carried out varying the number of steps,  $n$ : 100, 1000, 10000 and the results were extrapolated for  $n \rightarrow \infty$ .

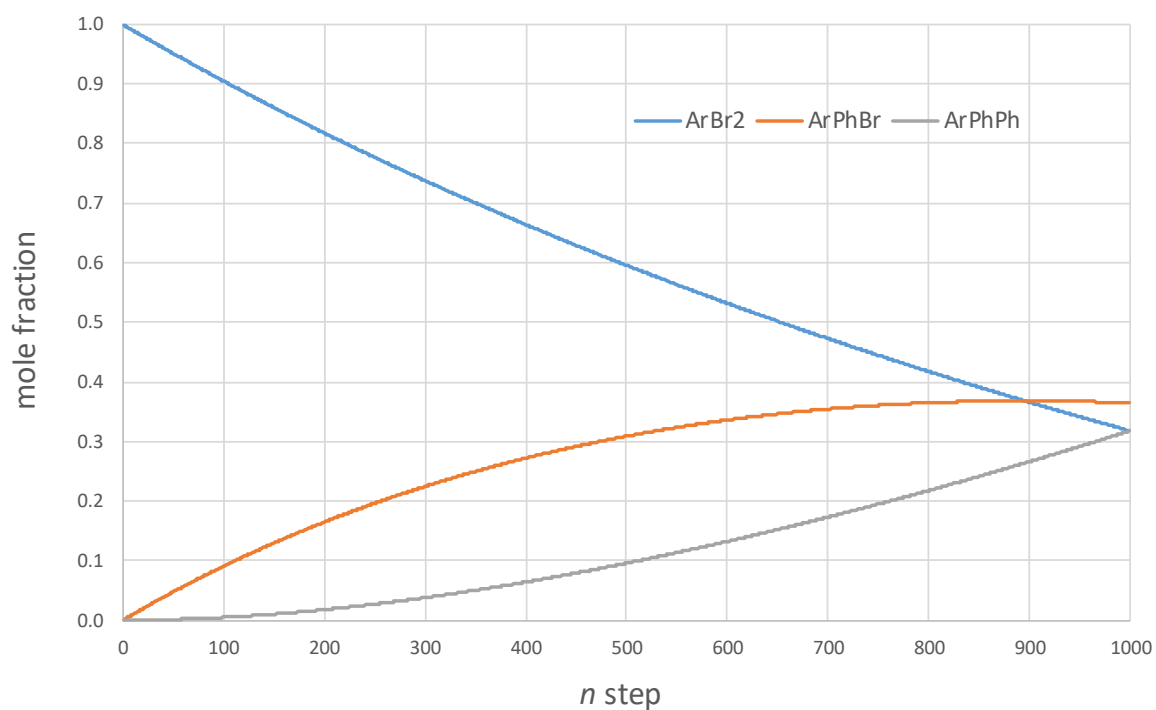
A similar analysis was done by dropping the condition  $k(\text{ArBr}_2) = 2 \cdot k(\text{ArPhBr})$  and considering  $k(\text{ArBr}_2) = k(\text{ArPhBr})$ , i.e. more Br atoms do not lead to faster reaction.

Figure S1 shows the results of these calculations for the reaction between 1 mol/equiv of 1,4-dibromobenzene and 1 mol/equiv of phenylboronic acid. The same results are valid for all the other synthesis studied in this work involving a disubstituted halobenzene.

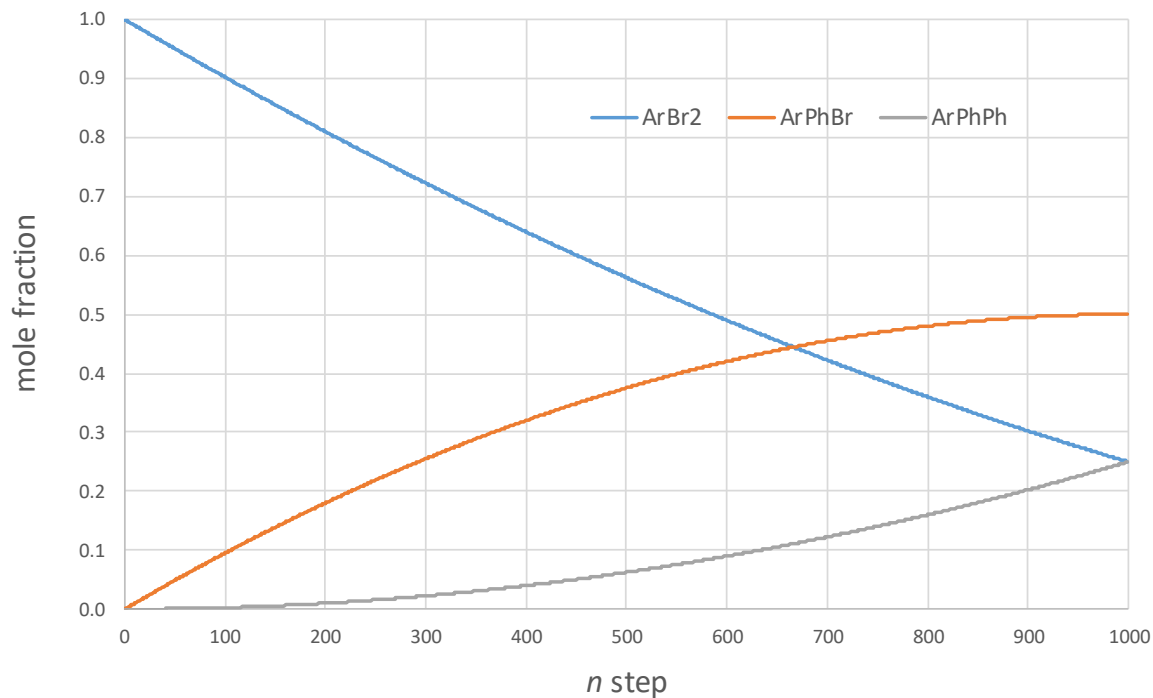
The results for the calculated (ArBr<sub>2</sub> / ArPhBr / ArPhPh) selectivity are 32/36/32, if  $k(\text{ArBr}_2) = k(\text{ArPhBr})$ , and 25/50/25, if  $k(\text{ArBr}_2) = 2 \cdot k(\text{ArPhBr})$ .

Alternatively, a simpler estimation can be done by applying the steady-state approximation for the monosubstituted intermediate. In this context, equal reaction rates for the coupling reactions of ArBr<sub>2</sub> and ArPhBr would give a 33/33/33 ratio, while double reaction rate for ArBr<sub>2</sub> would give a 25/50/25 ratio. These ratios are similar to the ones derived above from the step-iteration method. However, the rigorous kinetic analysis of the Suzuki reaction for two consecutive coupling cycles is considerably complex and falls outside the scope of this work.

**A)  $k(\text{ArBr}_2) = k(\text{ArPhBr})$**



**B)  $k(\text{ArBr}_2) = 2 \cdot k(\text{ArPhBr})$**



**Figure S1.** – Plot of the simulated mole fraction evolution of products and reagent for the reaction between 1,4-dibromobenzene and phenylboronic acid in 1:1 stoichiometry, considering A) equal rate constants and B) attack to ArBr<sub>2</sub> is faster due to having twice the Br atoms;  $n = 1000$  steps.

### S3. Additional Suzuki-Miyaura reactions

**Table S2.** Results for the Suzuki-Miyaura reactions between 2,5-dibromothiophene or 1,1'-dibromoferrrocene and phenylboronic acid. Selectivity in mol %.

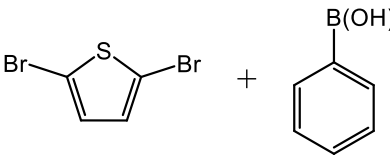
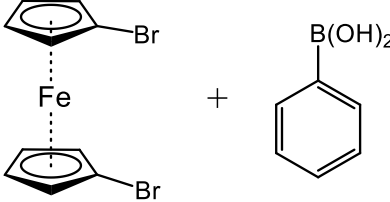
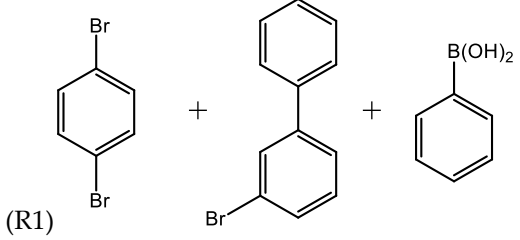
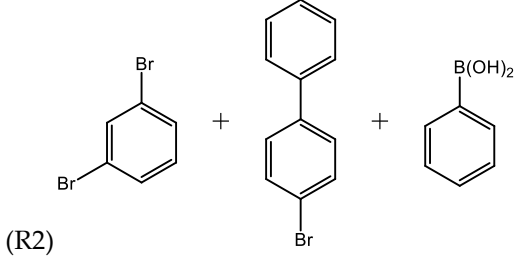
Reaction	Conditions	Selectivity % ArBrBr/ArBrPh/ArPhPh h	Ratio ArPhPh/ArBrPh h
	Pd(OAc) <sub>2</sub> (3 mol %)  H <sub>2</sub> O/DMF (1:1) V <sub>total</sub> = 20 mL	88/5/6	1.2
	K <sub>2</sub> CO <sub>3</sub> (1.4 equiv)  T = 70 °C  4 h	70/14/16	1.1

Table S3 presents the results of two competing Suzuki reactions. These were done to demonstrate that there is no significant difference in reactivity between the dibromo reactant ArBr<sub>2</sub> and the mono-substituted ArArBr intermediate. These reactions were carried out under the same experimental conditions of the other reactions (tables 1 – 3 of the main manuscript). The two reactions were needed to evaluate the intrinsic differentiation in reactivity due to the *meta*- and *para*- positions in the brominated reactants. As expected, the results in table S3 show that, apart from this *meta/para* differentiation, there is no significant difference between the reactivity of ArBr<sub>2</sub> and ArArBr in Suzuki-Miyaura coupling. To remove the limitation associated to the different intrinsic reactivities of the *meta*- and *bromo*- species, the competing reactions between *para*-dibromobenzene and 4-bromobiphenyl were also carried out and the results are presented in Table S4. The results in Tables S3 and S4 confirm the similar reactivity of the dibromo and monobromo substrates towards oxidative addition, for both the catalysts Pd(OAc)<sub>2</sub> and Pd-PEPPSI-*i*Pr. These observations support that the preference for the bis-coupling product in the Suzuki reaction cannot be attributed to a greater reactivity of the mono-substituted intermediate (relative to the dibromo reactant).

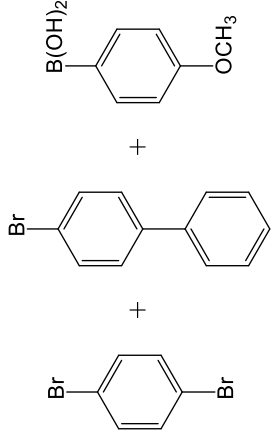


**Table S3.** Results for the two Suzuki-Miyaura competition reactions between (R1) *para-/meta*-dibromobenzene and (R2) *meta-/para*-bromobiphenyl; reaction conditions were the same for both reactions. Selectivity in mol %.

Reaction	Conditions	Selectivity, mol % <sup>a</sup>			
		ArBr <sub>2</sub>	ArArBr	ArArAr	
				<i>meta-</i>	<i>para-</i>
(R1) 	1 mol equiv of each reactant Pd(OAc) <sub>2</sub> (3 mol %) H <sub>2</sub> O/DMF(1:1) V <sub>total</sub> = 20 mL	16	41	17	26
(R2) 	K <sub>2</sub> CO <sub>3</sub> (1.4 equiv) T = 70 °C 4 h	15	45	27	13

<sup>a</sup> ArBr<sub>2</sub> denotes the *meta*- or *para*-dibromobenzene, ArArBr the *meta*- or *para*-bromobiphenyl (in this case it was not possible to separate the GC peaks of the two compounds and the mol % reported correspond to the sum of the two isomers), and ArArAr the *meta*- or *para*-terphenyl.

**Table S4.** Results for the two Suzuki-Miyaura competition reactions between *para*-dibromobenzene and *para*-bromobiphenyl with 4-methoxyphenylboronic acid, using Pd(OAc)<sub>2</sub> and Pd-PEPPSI-iPr; reaction conditions were the same for both reactions. Selectivity in mol %.

Reaction	Catalyst	Selectivity, mol % <sup>a</sup>				
		Reactants		Products	Mono-intermediate	Homocoupling
		Br-Ar-Br	Br-Ar-Ar			
 <p>1 mol equiv of each reactant catalyst (3 mol %) H<sub>2</sub>O/DMF(1:1), V<sub>total</sub> = 20 mL K<sub>2</sub>CO<sub>3</sub> (1.4 equiv) T = 70 °C 4 h</p>	Pd(OAc) <sub>2</sub>	33	40	CH <sub>3</sub> O-Ar-Ar-Ar-OCH <sub>3</sub> 10	CH <sub>3</sub> O-Ar-Ar-Br 4	CH <sub>3</sub> O-Ar-Ar-OCH <sub>3</sub> 6
	Pd-PEPPSI-iPr	31	40	12	12	2