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Highlights on the General Preference for Multi-Over Mono-Coupling in the Suzuki–Miyaura Reaction

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Abstract: A systematic synthetic study was performed to explain the usual trend in selectivity towards multi-coupling, over mono-coupling, in Suzuki–Miyaura reactions. This preference was observed under different reaction conditions: for various halobenzenes, using substituents on the boronic acid, and changing the catalyst and temperature. Moreover, this reaction selectivity was found to increase for more reactive systems towards oxidative addition and more diluted media. The results constitute experimental evidence that the formation of the totally substituted coupling product is kinetically favoured by a reaction path location—the proximity between the regenerated catalyst and the newly formed coupling intermediate promotes the subsequent reaction.

Keywords: oxidative addition; organocatalysis; Pd catalyst; multi-coupling; reaction selectivity



Citation: Lima, C.F.R.A.C.; Lima, M.A.L.; Pinto, J.R.M.; Ribeiro, M.G.T.C.; Silva, A.M.S.; Santos, L.M.N.B.F. Highlights on the General Preference for Multi-Over Mono-Coupling in the Suzuki–Miyaura Reaction. *Catalysts* **2023**, *13*, 928. <https://doi.org/10.3390/catal13060928>

Academic Editor: Laura Antonella Aronica

Received: 22 April 2023

Revised: 18 May 2023

Accepted: 23 May 2023

Published: 24 May 2023



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1. Introduction

The Suzuki–Miyaura cross-coupling has established itself as one of the most iconic and ubiquitous reactions in Chemistry [1–4]. Its importance for the scientific community became clear when A. Suzuki was awarded the joint Nobel Prize in Chemistry in 2010 “for palladium-catalysed cross-couplings in organic synthesis” [5,6]. The most attractive feature of this synthetic approach is probably the ease with which new C–C bonds can be formed between a myriad of readily accessible coupling partners. Despite the routine usage of Suzuki–Miyaura coupling in numerous laboratories all around the world, its reaction mechanism is quite complex and still hides subtle quirks yet to be understood. One of the most famous topics of discussion concerns the role of the base in the transmetalation step [7–13]. Another well-known subject regards the synthetic versatility of unsymmetrical coupling, such as in the synthesis of unsymmetrical triaryls from dihaloarenes, and the different strategies used to achieve it [14–23]. In general, a high selectivity for multi-over mono-coupling is observed and particular reaction conditions are required to achieve good yields of the unsymmetrical coupling products [23–31]. Strategies such as using less molar equiv of the boronic acids/esters, using unsymmetrical dihalobenzenes, and sequential addition of reactants have been reported [14–23]. Still, this counter-statistical and counter-intuitive outcome towards multi-coupling is the observed result under many reaction conditions and cannot be explained by typical reactivity arguments (e.g., electronic effects, stereochemistry, stability of reaction intermediates) [23–35]. This preferential oxidative addition in Pd-catalyzed Suzuki–Miyaura cross-coupling was investigated by Dong and

Hu [34]. The authors studied the reactions of dihaloarenes with arylboronic acids and obtained a high disubstituted/monosubstituted product ratio for most of the dihaloarenes tested. They explained this reaction outcome by recalling that, after reductive elimination, the monosubstituted product is formed near the regenerated Pd(0) catalyst. A subsequent oxidative addition, faster than the diffusion of the monosubstituted species away from Pd(0), then explains the preference for the disubstituted product [34]. Scherf and co-workers had also observed this preferential oxidative addition in the cross-coupling reaction of 2,7-dihalofluorenes with 1 equiv of arylboronic acid [31]. Subsequently, Schmitz and Höger verified a similar preference for the fully substituted product in the Suzuki reaction between a diiodo-monobromo-quinquephenylene and an aryl boronic acid [29], showing that this preference can take precedence over the usual bromo/iodo selectivity. The existence of a preferential oxidative addition is also highly relevant in the control of cross-coupling polymerizations [35–43]. These reactions consist in many successive catalytic cycles and thus the process of chain growth depends on the readiness with which the newly formed coupling product reacts with the Pd catalyst again. Despite the relevance of such a general mechanistic feature in catalysed cross-coupling reactions, this proximity effect is rarely mentioned while interpreting the results of such syntheses. Herein, to extend on these findings, we present a systematic synthetic study to explore the impact of such transient reaction proximity (between the substituted intermediate and the catalyst) on the selectivity of Suzuki–Miyaura cross-coupling of di- and trihaloarenes.

2. Results and Discussion

Herein, we present a systematic study on the Suzuki reaction of halobenzenes with phenylboronic acid to evaluate reaction selectivity in terms of mono-coupling vs. multi-coupling. The synthetic strategy can be divided into three main approaches regarding the following effects on reaction selectivity: (a) position of the leaving groups (*ortho*, *meta*, *para*); (b) identity of the leaving groups (Br and I); (c) a number of leaving groups (syntheses with di- and trihalobenzenes). In combination with this methodology, the effects of reactant concentration, catalyst [Pd(OAc)₂, Pd(PPh₃)₄, and Pd-PEPPSI-iPr], temperature (0 and 70 °C), electron-withdrawing and electron-donating substituents in the boronic acid, and stoichiometry were also investigated. The experimental results are presented in Tables 1–3. The biphenyl by-product (from the homocoupling of the phenylboronic acids) was observed in all syntheses, with a molar fraction in the final mixture from 3 to 15 mol%.

2.1. Reactivity Trends in the Dibromobenzenes

The first striking observation that can be drawn from Table 1 is the non-statistical outcome of reaction selectivity. The bis/mono ratio, or 4/3 ratio in Tables 1 and 2, can be interpreted directly as the preference for bis- over mono-coupling—a larger ratio indicates grater preference for the bis-coupling product. Given the 1:1 stoichiometry of the two reactants (1 and 2), simple calculations predict a selectivity for 1/3/4 of 32/36/32 (assuming the equal probability of attack to 1 and 3) or 25/50/25 (if considering that 1 has twice the Br atoms) (details in Supplementary Materials). As can be observed, most reactions show a large deviation from this statistical ratio, with a great preference for the formation of the bis-coupled product 4. This indicates that some significant factor in the reaction mechanism is increasing the reactivity of 3 relative to 1.

Interestingly, the effect of concentration follows a clear pattern—selectivity towards the bis-coupling product 4 increases (greater 4/3 ratio) for more diluted media (entries 1 vs. 2, 11–13, 14 vs. 15, and 20 vs. 21). In terms of halobenzene structure, it can be observed that the lowest preference for 4 (closer to the statistical ratio) is observed for the *ortho*-derivative, which is the least reactive of the three towards oxidative addition [3,44–46]. Increasing the stoichiometry of the dibromo reagent (entries 12 vs. 16) only increases its quantity in the final mixture, with virtually no effect on the 4/3 ratio.

Table 1. Results for the Suzuki–Miyaura reactions between *ortho*-, *meta*- or *para*-dibromobenzene and phenylboronic acid (effect of position). Selectivity in mol%, the quantity of catalyst used is 3 mol% (relative to the dibromo reagent), unless otherwise noted.

Entry	1 (mol Equiv.) 1	R	V _T ² /mL	Catalyst	T/°C	Selectivity% 1/3/4	Ratio 4/3
1	<i>o</i> -diBrBz (1:1)	–H	60	Pd(OAc) ₂	70	56/9/35	3.9
2	<i>o</i> -diBrBz (1:1)	–H	20	Pd(OAc) ₂	70	49/20/31	1.5
3	<i>o</i> -diBrBz (1:1)	–H	20	Pd(OAc) ₂	0	74/11/15	1.3
4	<i>o</i> -diBrBz (1:1)	–H	20	Pd(PPh ₃) ₄	70	50/25/25	1.0
5	<i>o</i> -diBrBz (1:1)	–H	20	Pd(PPh ₃) ₄	0	37/40/23	0.6
6	<i>o</i> -diBrBz (1:1)	–H	20	Pd(PPh ₃) ₄ 0.1 mol%	70	81/8/11	1.4
7	<i>o</i> -diBrBz (1:1)	–H	40	Pd-PEPPSI-iPr	70	75/8/17	2.0
8	<i>o</i> -diBrBz (1:1)	–H	20	Pd-PEPPSI-iPr	70	59/12/29	2.3
9	<i>o</i> -diBrBz (1:1)	–H	20	Pd-PEPPSI-iPr	0	90/6/4	0.6
10	<i>m</i> -diBrBz (1:1)	–H	20	Pd(OAc) ₂	70	51/9/40	4.6
11	<i>p</i> -diBrBz (1:1)	–H	40	Pd(OAc) ₂	70	54/3/43	14.8
12	<i>p</i> -diBrBz (1:1)	–H	20	Pd(OAc) ₂	70	57/7/36	5.2
13	<i>p</i> -diBrBz (1:1)	–H	10	Pd(OAc) ₂	70	50/11/39	3.6
14	<i>p</i> -diBrBz (1:1)	–H	40	Pd(OAc) ₂	0	54/5/41	8.0
15	<i>p</i> -diBrBz (1:1)	–H	10	Pd(OAc) ₂	0	56/7/38	5.4
16	<i>p</i> -diBrBz (2:1)	–H	20	Pd(OAc) ₂	70	71/5/24	5.4
17	<i>p</i> -diBrBz (1:1)	–H	40	Pd(OAc) ₂ 60 mol%	70	61/6/33	5.5
18	<i>p</i> -diBrBz (1:1)	–H	20	Pd(PPh ₃) ₄	70	50/7/43	6.6
19	<i>p</i> -diBrBz (1:1)	–H	20	Pd(PPh ₃) ₄	0	58/8/34	4.0
20	<i>p</i> -diBrBz (1:1)	–H	40	Pd-PEPPSI-iPr	70	63/3/34	11.8
21	<i>p</i> -diBrBz (1:1)	–H	20	Pd-PEPPSI-iPr	70	43/6/51	8.8
22	<i>p</i> -diBrBz (1:1)	–H	20	Pd-PEPPSI-iPr	0	69/3/28	9.8
23	<i>p</i> -diBrBz (1:1)	–OCH ₃	20	Pd(OAc) ₂	70	51/10/38	3.7
24	<i>p</i> -diBrBz (1:1)	–OCH ₃	20	Pd-PEPPSI-iPr	70	56/7/37	5.6
25	<i>p</i> -diBrBz (1:1)	–CHO	20	Pd(OAc) ₂	70	44/24/32	1.3
26	<i>p</i> -diBrBz (1:1)	–CHO	20	Pd-PEPPSI-iPr	70	58/10/32	3.1

¹ 1:2 stoichiometry. ² Total volume V(H₂O + DMF), V(H₂O) = V(DMF).

Preferential formation of the bis-product is observed for all the catalysts studied. For the syntheses with *p*-dibromobenzene (*p*-diBrBz), the preference for bis-coupling is obvious for all the catalysts tested (e.g., entries 12 vs. 18 vs. 21 at 70 °C). However, some syntheses with the less reactive *o*-dibromobenzene (*o*-diBrBz) show outcomes much closer to the statistical predictions, with special emphasis on Pd(PPh₃)₄ and Pd-PEPPSI-iPr at 0 °C. The presence of phosphine ligands in the Pd catalyst has been associated with lower catalytic efficiency [46–48]. In contrast, Pd precatalysts with *N*-heterocyclic carbene (NHC) ligands, such as Pd-PEPPSI-iPr, have been known to promote oxidative addition and reductive elimination (due to strong σ-donation to Pd and variable steric bulk), and to facilitate the cross-coupling between less reactive species [43,49–53]. In addition, these precatalysts are generally stable to moisture and air [49–51]. However, the results of entry 9 suggest a significant decrease in catalytic efficiency of Pd-PEPPSI-iPr at low temperatures, with the low 4/3 ratio being accompanied by a very limited conversion of the initial reagent.

Moreover, in general, the results showed a lower conversion of the dibromo reagent if using Pd-PEPPSI-iPr.

Table 2. Results for the Suzuki–Miyaura reactions between a *para*-dihalobenzene and phenylboronic acid (effect of leaving group). Selectivity in mol%.

Entry	X ¹	V _T ² /mL	T/°C	Selectivity% 1/3/4	Ratio 4/3
1	Br/Br ³	20	70	57/7/36	5.2
2	Br	20	70	21/19/60	3.2
3	Br	10	70	23/22/55	2.5
4	Br	20	0	50/6/44	7.5
5	I	20	70	47/3/50	19.3

¹ The 1:2 stoichiometry is of (1:1) in all cases. ² Total volume V(H₂O + DMF), V(H₂O) = V(DMF). ³ The results for *p*-diBrBz are also presented for comparison.

Table 3. Results for the Suzuki–Miyaura reactions of *ortho*-, *meta*- or *para*-dibromobenzene with phenylboronic acid (effect of number of leaving groups). Selectivity in mol%.

Entry	1 (mol Equiv.) ¹	V _T ² /mL	Catalyst	T/°C	Selectivity% 1/3/4/5
1	1,3,5-triBrBz (1:1)	20	Pd(OAc) ₂	70	64/2/2/33
2	1,3,5-triBrBz (1:1)	10	Pd(OAc) ₂	70	62/1/2/34
3	1,3,5-triBrBz (1:1)	20	Pd(OAc) ₂	0	67/1/0/33
4	1,3,5-triBrBz (1:2)	20	Pd(OAc) ₂	70	32/2/2/64
5	1,3,5-triBrBz (1:1)	20	Pd-PEPPSI- iPr	70	69/1/1/30
6	1,2,4-triBrBz (1:1)	20	Pd(OAc) ₂	70	52/17/10/21
7	1,2,4-triBrBz (1:1)	20	Pd(OAc) ₂ ³	70	58/16/9/17

¹ 1:2 stoichiometry. ² Total volume V(H₂O + DMF), V(H₂O) = V(DMF). ³ In this case 7 mol% of Pd(OAc)₂ was used.

These observations follow the idea that the preferential formation of the bis-product becomes more significant in conditions of greater reactivity (e.g., higher temperature and sterically unhindered systems). We also tested the effect of using a very small quantity of catalyst [entry 6 with 0.1 mol% of Pd(PPh₃)₄] and of a much larger quantity [entry 17 with 60 mol% of Pd(OAc)₂]. Interestingly, the results suggest that using less catalyst increases the 4/3 ratio (higher preference for bis-coupling; entries 4 vs. 6 and 11 vs. 17), although, as expected, the reaction conversion is severely reduced if using residual quantities of catalyst (entries 4 vs. 6).

Of the catalysts studied, Pd-PEPPSI-iPr is the one that shows the largest decrease in catalytic efficiency with decreasing temperature. However, the 4/3 ratio is marginally affected in the reaction with *p*-diBrBz (entries 21 vs. 22), probably because the decrease in reactivity with temperature is less pronounced (if compared to the less reactive *o*-diBrBz). Note that diffusion also becomes slower with decreasing temperature. Interestingly, the catalytic efficiency of Pd(PPh₃)₄ is similar at both temperatures. With this catalyst, the effect of temperature is more obviously manifested on the final product distribution, with the 4/3 ratio increasing at higher temperatures. Actually, the selectivity for entries 4 and 5 is very close to the expected statistical outcome. One can infer that as more factors that reduce reactivity are presented [e.g., *o*-diBrBz, Pd(PPh₃)₄, low temperature], the more the reaction outcome will approach the statistical ratio (ignoring other sources of intrinsic reactivity, such as electronic effects, solvation, etc.). For the other two catalysts, lower temperature tends to decrease the total conversion of the dibromo reagent, but the impact on the 4/3 ratio is less significant. In these cases (entries 3, 9, 15, and 22), competing side reactions (such as homocoupling and hydrolytic deboronation of the boronic acid) may become more important at low temperatures.

The effect of substituents on the boronic acid (entries 23–26) is quite interesting. Firstly, the preferential formation of the bis-coupling product is observed for all the substituents studied. However, relative to R = –H, this preference is less pronounced for both the electron-donating (EDG), –OCH₃, and electron-withdrawing (EWG), –CHO, groups. While the effect of the electron-donating –OCH₃ in the reaction outcome is small, the electron-withdrawing –CHO significantly decreases the 4/3 ratio. For both groups, selectivity towards the bis-coupling product is lower if using Pd(OAc)₂, comparatively to Pd-PEPPSI-iPr. EWGs in the aryl halide increase the electrophilicity of this species and this shall, in principle, increase its reactivity towards oxidative addition with Pd [3,45]. Does solvation of the more hydrophilic –CHO intermediates play a role? Further studies are needed to discuss these results in more detail.

2.2. Reactivity Trends in Iodobenzene Derivatives

The iodobenzene derivatives were used to study the effect of the leaving group ability on reaction selectivity. Despite the greater lability of iodine [3,44–46], the results presented in Table 2 also show a marked preference for the bis-coupled product 4. The selectivity observed for *p*-diiodobenzene (entry 5) follows the results of its bromine analogue (entry 1), although the greater reactivity, towards oxidative addition, of the iodine compound seems to enhance the preference for bis-coupling even more. On the other hand, the results for 1-bromo-4-iodobenzene (entries 2–4) evidence some significant differences relative to the general trend observed so far. The syntheses carried out at 70 °C (entries 2 and 3) show a significantly higher proportion of the mono-coupled product 3 when compared to the other entries in this table, and with the results in Table 1 for *p*-dibromobenzene. A possible explanation is the difference in reactivity between the two halogens (note that no traces of 3 with X = I were observed by GC), which favours substitution of I over Br and contributes for a more extensive conversion of 1-bromo-4-iodobenzene. Temperature has a pronounced effect in the reactions of bromiodobenzene (entries 2 vs. 4, Table 2), with lower *T* leading to a smaller conversion of 1 and increasing the 4/3 ratio. Lower reactivity of aryl iodides at lower temperatures, under classical Suzuki coupling conditions, was reported by Bissember and co-workers [47]. The authors report an inefficient coupling of

aryl iodides at low temperatures ($\approx 50^\circ\text{C}$) in the presence of Pd/ PPh_3 catalyst systems. Hence, it is reasonable to assume that, under the reaction conditions reported in Table 2, the Br vs. I coupling in 1-bromo-4-iodobenzene is less favoured towards iodine at 0°C than it is at 70°C . Some care should be taken concerning the mol% of **1** (1-bromo-4-iodobenzene) in entries 2 and 3 of Table 2. Given that only 1 mol equiv of boronic acid was used, the mol% of around 20 for **1** is intriguing and contradicts simple mass balance calculations. We suggest that the lower molar fraction of **1** is due to some decomposition at higher temperatures (note that at $T = 0^\circ\text{C}$, entry 4, the molar fractions are consistent). In most reactions studied in this work, mass balance calculations are consistent with the fact that a small fraction of phenylboronic acid reacts via homocoupling, forming biphenyl.

In consonance with the results presented in Table 1, dilution of the reaction medium has the effect of enhancing the selectivity towards bis-coupling (entries 2 vs. 3). It is, however, worth noting that even in the presence of a reactivity gradient like $-\text{Br}$ vs. $-\text{I}$, the reaction still shows a large selectivity towards the bis-coupling product **4**.

2.3. Reactivity Trends in Tribromobenzenes

Table 3 shows the effects on reaction selectivity of adding one more $-\text{Br}$ leaving the group to the dibromo reactant (results for two tribromobenzenes). As before, the effect of concentration, although residual, appears to follow the same trend and temperature has a very small effect on selectivity. Likewise, the system with greater steric effects (1,2,4-triBrBz), and thus less reactive, shows a less pronounced selectivity towards the formation of the fully substituted product **5**. If using 1,3,5-triBrBz, the amount of the intermediates **3** and **4** is very small, even if the stoichiometry of the boronic acid is doubled (entry 4). The same trend is observed in switching the catalyst to Pd-PEPPSI-*i*Pr (entry 5).

Doubling the stoichiometry of the boronic acid only increases the conversion of the tribromo reagent (entries 1 vs. 4). Increasing the amount of catalyst (entries 6 vs. 7) had no significant effect on selectivity.

To confirm that less reactive systems lead to lower selectivity (closer to the statistical outcome), we carried out two additional syntheses, under identical experimental conditions (the same as, for example, entry 2 in Table 1) using 1,1'-dibromoferrocene and 2,5-dibromothiophene. Due to their lower electrophilicity, these systems are less reactive towards oxidative addition [3,44–46], which was supported herein by the lower conversion of the dibromo species, and the higher fraction of biphenyl formed. The results (details in the Supplementary Materials) corroborate the trend in selectivity, with these systems showing bis/mono ratios much closer to the statistical prediction.

As reported by Choi and coworkers [35], the use of Buchwald ligands with the Pd_2dba_3 catalyst in Suzuki–Miyaura syntheses with 2,5-dibromothiophene increases the ratio of the disubstituted product relative to the mono-intermediate. These results go in line with our findings. Like the catalysts used in this work, Pd_2dba_3 seems not that effective in increasing the reactivity towards oxidative addition of the less reactive bromothiophenes, and thus the mono-intermediate is formed in higher proportions. The use of the highly active Buchwald ligands [54–56] shall increase this reactivity and with it the ratio of the bis-coupling product. The authors also observed that dilution of the reaction medium further increases the selectivity of the disubstituted product [35], in nice agreement with our findings.

2.4. Reaction Proximity Effect of the Catalyst

The results showed, in accordance with previous findings [23–31,34], a marked selectivity towards the multi-coupling, fully substituted, Suzuki product. This selectivity was found to depend on the concentration and on the reactivity of the halogenated reactants towards oxidative addition, being further enhanced in more diluted media and for more reactive systems. The reactions presented in section S3 (Table S3) of the Supplementary Materials corroborate that the preference for the multi-coupling product is not due to the greater reactivity of the substituted intermediates relative to the unsubstituted reactant.

These results show that, as expected, the intrinsic reactivity towards oxidative addition of, for instance, 1,4-dibromobenzene and 4-bromobiphenyl, is similar. Moreover, as already evidenced by other authors [24,26,29,31,34], these patterns in reaction selectivity cannot be adequately described by typical thermodynamic or mechanistic considerations (e.g., relative stability and/or reactivity of the species involved, inductive, and mesomeric effects). Instead, all the experimental observations can be explained by a reaction kinetic pathway that is favoured by proximity effect or reaction path location. The last step of the catalytic cycle (reductive elimination) involves the liberation of the coupling product together with the regenerated catalyst. Hence, both species are formed very close to each other in solution and, if there are more halogens to react, it is logical to assume that a subsequent reaction between them will be highly favoured (see Figure 1). Selectivity decreases with an increase in concentration because there are more molecules of the unsubstituted halogenated reactant to compete for the catalyst in its vicinity. Lower selectivity is observed for less reactive compounds because the mono-substituted intermediate has more chances of diffusing away through the solution before reacting again. The effect of concentration on reaction selectivity should, however, be interpreted with care. One cannot exclude the possibility of changing the nature of the active catalyst species (e.g., dissolved molecular complex, colloids, or larger metal particles) resulting from a dilution or the amount of catalyst used [57,58]. Going from homogeneous to heterogeneous catalysis, or vice-versa, will probably affect the relative importance of the proximity effect on the reaction mechanism, thus altering the ratio of the products. This is particularly important in those reactions where significantly different amounts of catalyst were used (Table 1, entries 6 and 17). However, the regular decrease in the 4/3 ratio with increasing concentration observed in various entries of Table 1 (entries 1 vs. 2, 11–13, 14 vs. 15, and 20 vs. 21) is a strong suggestion that no abrupt change in the nature of the catalyst occurs within this concentration range.

The effect of temperature is twofold: higher temperature will probably increase reactivity (favouring the multi-coupled product), but also increases diffusivity in solution (favouring the incompletely substituted intermediates). These factors play in opposite directions, and thus the perceived effect of temperature is generally small. The results for entries 2–4 (Table 2) are explained by the interplay of two effects that push in opposite directions: reaction proximity favours 4, while the best leaving group ability of iodine favours 3. At $T = 0\text{ }^{\circ}\text{C}$, the rate of iodine oxidative addition shall decrease significantly, and reaction proximity becomes the major effect.

The existence of such a preferential oxidative addition in Suzuki coupling reactions was addressed before by Dong and Hu [34], and discussed by other authors [29,31]. This work extends on their findings, highlighting the importance of the reaction proximity effect in catalysed reactions and giving new insights about its implications on reaction outcomes.

Although the phenomenon of “catalyst transfer polycondensation” (CTP) [35,41–43,59,60], and its ramifications to various types of cross-coupling reactions, including Suzuki–Miyaura, are typically evoked in the context of polymers, one cannot ignore the resemblance of CTP with preferential oxidative addition. Either by the proximity of the catalyst to the newly formed coupling intermediate or some kind of ring-walking phenomenon [61], the result is the same—to promote multi-coupling in the reaction.

The reasons for choosing DMF as a solvent in this study are the following: (i) it is a typical solvent for Suzuki–Miyaura reactions; (ii) it has relatively low volatility, ensuring that the solvent composition is maintained during the reactions at high temperatures (acetone is an example of a bad choice here); (iii) it is completely miscible with water, affording a homogeneous medium for the reaction (toluene is an example of a bad choice here); in this study, we wanted to avoid the additional complexity associated with heterogeneous synthesis; and (iv) in all syntheses, the 1:1 mixed solvent with water was able to completely dissolve all the reactants in the initial reaction mixture, ensuring a homogeneous starting point for the synthetic study. In this work, we focused on the effect of the identity of the halobenzene and boronic acid, dilution, and catalyst. We recognize, however, that a fully comprehensive synthetic study of preferential oxidative addition in Suzuki–Miyaura

cross-coupling should include testing more solvents. Being quite a complex topic, the effect of solvent deserves, in our opinion, a paper of its own.

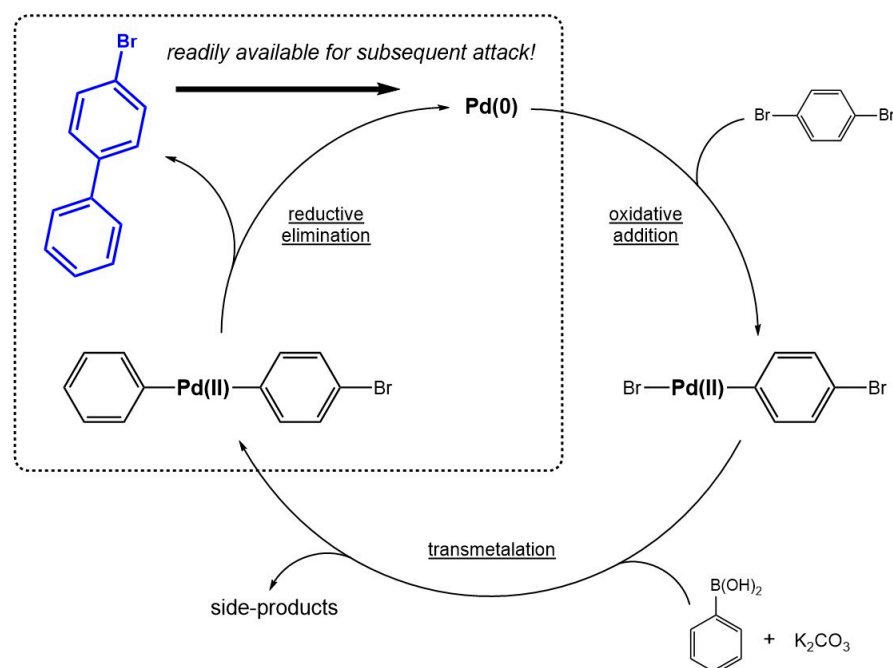


Figure 1. Scheme evidencing the favoured oxidative addition of the first coupling product due to the proximity between both reactants, 4-bromobiphenyl and Pd(0) catalyst, immediately after their formation.

3. Materials and Methods

All reagents and solvents were purchased from commercial sources and used as supplied. The syntheses were carried out as follows (stoichiometry, the volume of solvent, temperature, and catalyst may change): a mixture of the appropriate halobenzene (0.50 mmol), phenylboronic acid (0.50 mmol), and catalyst (3 mol%, unless otherwise noted) in DMF (10 mL) was prepared in a round bottom flask and heated at 70 °C (or cooled to 0 °C) under stirring (500 rpm). After complete dissolution and temperature stabilization, a solution of K_2CO_3 (0.70 mmol) in water (10 mL) was added and the reaction was stirred for 4 h. The final mixture was left to reach room temperature and extracted with CH_2Cl_2 . The organic phase was washed with water and aqueous NaOH and dried over anhydrous Na_2SO_4 . An aliquot of this final organic solution was injected in the GC chromatograph for selectivity analysis. The solvent was then removed by evaporation and a mixture of products was obtained. All GC analyses were performed on an HP 4890 apparatus equipped with a HP-5 column, cross-linked, diphenyl (5%), and dimethylpolysiloxane (95%), length = 15 m, inner diameter = 0.530 mm, film thickness = 1.50 μm , and a FID detector. Care was taken to ensure that the final CH_2Cl_2 organic phase was homogeneous, and no precipitates or suspensions were present. Sample injections of 1 μL were made through a microsyringe. Reaction selectivity was evaluated by analysis of the full chromatograms; all the relevant reagents, products, and byproducts of the Suzuki reaction (unreacted halobenzene, biphenyl, and coupling products) could be detected and quantified in this way. Unreacted boronic acids were only observed in those cases where washing of the organic phase with aqueous NaOH was not performed. To convert the observed relative peak areas into relative% mol fractions, calibration injections were made using samples of known concentrations of each compound. These samples were prepared from the original synthesized or commercially purchased compounds to ascribe each peak to each given compound based on their retention times.

4. Conclusions

Herein, we provided strong experimental proof for the reaction proximity effect, or preferential oxidative addition, in Suzuki–Miyaura reaction. This effect favours the formation of multi-coupling products and will always be present in such catalysed systems. This mechanistic feature prevails under most of the reaction conditions tested in this study. Temperature, identity of the reactants, substituents, and catalyst appear to only matter to the extent they affect the reactivity of the aryl halide towards oxidative addition. The results showed that this preferential oxidative addition becomes more significant for more reactive systems (towards oxidative addition) and lower concentrations of the reactants. The outcome of the reaction thus depends on how effectively the mono-coupling intermediates diffuse away from the catalyst before reacting again. Hence, lower reactivity and higher concentration of the halogenated reactant are good starting points for favouring the mono-substituted cross-coupling product in asymmetric synthesis. The findings reported herein are an important contribution for understanding the mechanism and outcome of Suzuki–Miyaura reactions and can, in principle, be extrapolated to many other types of catalysed reactions in solution; Heck and Sonogashira reactions being close examples.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/catal13060928/s1>. Detailed GC analyses and statistical analysis of reaction selectivity; Table S1: GC calibration results; Figure S1: Plot of the simulated mole fraction evolution of products and reagent; Table S2: Results for the Suzuki–Miyaura reactions between 2,5-dibromothiophene or 1,1'-dibromoferrocene and phenylboronic acid; Table S3: Results for the two Suzuki–Miyaura competition reactions between (R1) *para*-/*meta*-dibromobenzene and (R2) *meta*-/*para*-bromobiphenyl; Table S4: Results for the two Suzuki–Miyaura competition reactions between *para*-dibromobenzene and *para*-bromobiphenyl with 4-methoxyphenylboronic acid, using Pd(OAc)₂ and Pd-PEPPSI-iPr.

Author Contributions: Conceptualization, C.F.R.A.C.L.; methodology, C.F.R.A.C.L. and M.A.L.L.; formal analysis, C.F.R.A.C.L. and M.A.L.L.; investigation, C.F.R.A.C.L., M.A.L.L. and J.R.M.P.; resources, M.G.T.C.R., A.M.S.S. and L.M.N.B.F.S.; data curation, C.F.R.A.C.L. and M.A.L.L.; writing—original draft preparation, C.F.R.A.C.L.; writing—review and editing, C.F.R.A.C.L., M.A.L.L., J.R.M.P., M.G.T.C.R., A.M.S.S. and L.M.N.B.F.S.; supervision, C.F.R.A.C.L. and L.M.N.B.F.S.; funding acquisition, M.G.T.C.R., A.M.S.S. and L.M.N.B.F.S. All authors have read and agreed to the published version of the manuscript.

Funding: The authors thank Fundação para a Ciência e Tecnologia (FCT), Lisbon, Portugal, European Social Fund (ESF), for financial support to the projects: (a) CIQUP, University of Porto (UID/QUI/0081/2020) and IMS, Institute of Molecular Sciences (LA/P/0056/2020); and (b) LAQV-REQUIMTE, Department of Chemistry, University of Aveiro (UIDB/50006/2020). The support from project UID/QUI/50006/2019 with funding from FCT/MCTES through national funds is also acknowledged. CFRACL is financed by national funds through the FCT-I.P., in the framework of the execution of the program contract provided in paragraphs 4, 5, and 6 of art. 23 of Law no. 57/29 August 2016, as amended by Law no. 57/19 July 2017.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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