



Supplementary Material: Kinetic study of the Herrmann-Beller palladacycle catalyzed Suzuki-Miyaura coupling of 4-iodoacetophenone.

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1. List of the tested homogeneous catalysts



Figure S1 List of the tested homogeneous catalysts.

2. Optimization of the reaction conditions

2.1. Selection of the catalyst

In order to study the kinetics of the homogeneous reaction, the catalyst should be soluble, active, stable without the formation of Pd black, and selective for the SM reaction.

Four homogeneous catalysts were tested in the SM coupling of 4-iodoacetophenone and phenylboronic acid (Table S1). PEPPSI (II) was active and selective giving 100% yield in bi-aryl in 1 hour transformed into Pd black very quickly which indicates that it was unstable at its molecular state. The same result was obtained for 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate (III): it was active, selective but it formed Pd black during the course of the reaction. The salicylaldehyde thiosemicarbazone palladium (II) chloride (IV) was inactive even at 100 °C for 1 h. Finally, the Herrmann-Beller palladacycle (I) showed the highest activity and selectivity without the formation of Pd black. Thus, I was selected to perform the kinetic study in this work.

Type of homogeneous catalysts	Pd black	Mean reaction rate* (molprod/molpd/min)	% yield	Solubility
Herrmann-Beller palladacycle (I)	None	24.2	100	+
PEPPSI [™] -IPr catalyst (II)	++	11.3	100	+
1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (III)	++	8.80	100	+
Salicylaldehyde thiosemicarbazone palladium(II) chloride (IV)	None	0	0 (<1)ª	+

Table	S1	Catalyst	selection	for	the	Suzuki-Miyaura	coupling	of	4-iodoacetophenone	with
pheny	lbor	onic acid .								

Conditions: 4-iodoacetophenone (1 mmol, 1eq.), phenylboronic acid (1.2 mmol, 1.2 eq.), K₂CO₃ (2 mmol, 2 eq.), ethanol (20 ml), 60 °C, 1 h stirring. I, II, III and IV (0.01 mmolrd). a: yield at 100 °C. *mean rate to reach 98% of yield.

2.2. Selection of the base

Seven bases were evaluated (Figure 2). Firstly, their solubility was tested. Three bases (K₂CO₃, K₃PO₄, and K₂HPO₃) were not soluble in ethanol at 0.1 M (2 eq.). In order to improve their solubility, a 9:1 ethanol:water mixture was used, in which the reacting solution was soluble whatever the conversion. K₂CO₃, K₃PO₄ allowed to reach high conversions, in contrast with K₂HPO₃.

The activity of soluble bases in ethanol (MeONa, NaOH, CH3COONa and NEt3) was tested in the same reaction at 60 °C for 1 h. Besides, only sodium methoxide and sodium hydroxide showed a good activity (Figure S2).

Finally, ethanol and MeONa were chosen because they showed the highest activity, and the mixture was homogeneous at room temperature, in contrast to sodium hydroxide that was active but required more mixing to be dissolved.



Figure S2 Choice of the base.

To conclude, the kinetic study of SM coupling of 4-iodoacetophenone and phenylboronic acid will be performed using Herrmann-Beller palladacycle (I), ethanol as solvent and sodium methoxide as a base.

The commercially available Herrmann-Beller palladacycle (I) has a crystalline form with quite large crystals. Dissolution in ethanol is rather slow and one must be cautious in order to avoid catalyst dissolution coupled to reaction kinetics. Thus I should initially be dissolved in toluene in which it dissolves easily, without forming Pd black for several days. Such issue is well illustrated by comparing conversion vs. time profiles of experiments where the catalyst is pre-dissolved and other where it is used as received, i.e. as crystals (Figure S3).

2 of 5

Thus, the catalyst initially dissolved in toluene with 5.80 10⁻⁵ mol_{Pd}/L gave the same kinetic profile as the directly used catalyst with a concentration ten times higher than the other one (4.48 10⁻⁴ mol_{Pd}/L) demonstrating that the dissolution kinetics may limit the apparent rate of reaction.



Figure S3 effect of palladacycle pre-dissolution in toluene. (a) brown squares: use of crystalline catalyst directly (5 10^{-4} mol_{Pd}/L); (b) green circles pre-dissolution of the catalyst in toluene (5 10^{-5} mol_{Pd}/L) and the (c) black triangles with pre-dissolution of the catalyst in toluene (5 10^{-5} mol_{Pd}/L). **Other conditions:** 4-iodoacetophenone (0.05 M, 1 eq.), phenylboronic acid (0.06 M, 1.2 eq.), MeONa (0.075 M, 1.5 eq.), T=60 °C, Ethanol (20 mL).

The use of toluene as the solvent for the catalyst dissolution could however lead to a micromixing problem between liquid phases (ethanol and toluene). Hence the measured kinetics might be limited by mass transfer between these phases. In order to check for micro-mixing issues, three tests were carried out: the first one using a batch reactor (20 mL), the second one using a flow reactor with a T-mixer and the last one using flow reactor with a commercial micromixer (SSIMM).

The yield vs. time profiles for three different reactors reveal negligible differences (Figure S4), which indicates the absence of mixing limitations. Therefore, it is confirmed that using these experimental conditions, the true reaction kinetics is measured.



Figure S4 Verification that the reaction is not limited by micro-mixing or mass transfer.

Conditions: 4-iodoacetophenone (0.025 M, 1 eq.), phenylboronic acid (0.03 M, 1.2 eq.), MeONa (0.038 M, 1.5 eq.), Pd (5 10⁻⁶ M, 0.0001 eq.), 60 °C. **Flow conditions:** flow rate from 0.3 mL/min to 1 mL/min, reactor length from 40 cm to 290 cm.

3. Example of reaction initial rate determination

The following method was followed to estimate the initial reaction rates:

- 1). Plot [P] = f(t)
- 2). Fit the concentration profile to 2 to 5-order polynoms and to C₀(1-exp(-kt).

3) Visually remove the worst fits if any. From the remaining ones, take a mean value of the x coefficient.

4)The error bar results from the variation between the methods Example:



Figure S5 method of initial rate determination.

In	this example:			
	x. coeff from 5 th order polynom	0,0052 mol/L/min		
	x. coeff from 4 th order polynom	0,0051 mol/L/min		
	x. coeff from 3 rd order polynom	0,0049 mol/L/min		
	x. coeff from exponential function	0,0048 mol/L/min		
	Mean value	0,0050 mol/L/min		
	Standard deviation	0,0002 mol/L/min		

5 of 5