Abstract: This article presents an experimental kinetic study of the Suzuki–Miyaura reaction of 4-iodoacetophenone with phenylboronic acid catalyzed by the Herrmann–Beller palladacycle. This catalyst, together with the solvent (ethanol) and the base (sodium methylate), were chosen to ensure catalyst stability and reactants solubility all along the reaction. Based on the study of initial reaction rates, a quasi-first-order was found for 4-iodoacetophenone with a first-order dependence on the initial concentration of palladium. A zero-order was found for the base and the phenylboronic acid. The oxidative addition step of the mechanism was thus considered as the rate determining step. A global rate law was derived and validated quantitatively. A global activation energy, with an average value of ca. 63 kJ/mol was determined.

Keywords: kinetics; Suzuki–Miyaura; palladacycle; activation energy; C–C coupling

1. Introduction

The Suzuki–Miyaura (SM) reaction, and more generally Pd carbon–carbon (C–C) cross-coupling reactions, have been the subject of numerous and prolific research in organic chemistry and catalysis [1] crowned by the 2010 Nobel Prize for Chemistry [2–5], awarded to Richard Heck, Ei-ichi Negishi, and Akira Suzuki. In the last decades, many authors have shown an interest in the mechanism [6–14], proposing different mechanisms that have the same basic elementary steps, but with detailed discussions about several key points such as the nature of the active species [7,12,15], the role of the base [16–18], the missing links in the transmetallation step [19], the rate-limiting step, and the solvent effect [14]. Despite the interest devoted to the mechanism and, more generally, to the reaction [1], very few publications provide global kinetic data and/or rate laws. Thus, the quantitative impacts of the different protagonists—catalyst, arylhalide, boronic acid, base, and temperature—are seldom available in a single rate law, albeit such impacts would be highly valuable for the design of production processes. Concerning the base, a very early report of a first-order rate law with respect to NaOH [20] but some more recent in-depth mechanistic studies have detailed its antagonistic impact, showing that a simple reaction order cannot describe its role [16,17]. The proposed reaction first order with respect to palladium [21,22] has deserved no controversy in the literature. In contrast, the reaction order with respect to the arylhalide is controversial. For example, a zero-reaction order with respect to arylbromide at 65 °C was published [20], whereas a first order towards arylhalide was recently published by Alfonso-Albinana et al. [22]. The quantitative temperature effect on the SM reaction was
reported only in two very recent papers. A global activation energy of 35 kJ/mol was determined for a polymer-based NHC-Pd-pyridine catalyst in aqueous media for the coupling of bromoacetophenone with phenylboronic acid [23] and 50 ± 5 kJ/mol for the coupling of bromoanisole with phenylboronic acid for a water-soluble palladium-β-cyclodextrin catalyst [24]. In the later, the absence of mixing and mass transfer issues was checked. The discrepancy between the values is high, due to the use of very different catalysts, but also to the lack of published kinetic studies, resulting in a lack of consensus. In addition to the complexity of the mechanism and the lack of global kinetics studies, other challenges relate to the difficulties to obtain reliable kinetic data. For example, in order to avoid a too complex reactor model, all reactants must be solubilized in the same solvent despite their somehow opposite solubility properties: the organohalides are well soluble in aprotic organic media, whereas organometallic boronic acid and the inorganic bases are more soluble in protic solvents and water; last, the solubility of the catalyst precursor is very dependent on its coordination sphere and ligand coordination. Moreover, considering the fast reaction rates for some Suzuki reactions, mass transfer limitations and mixing issues might have to be considered as well. In this work, the SM coupling of 4-iodoacetophenone with phenylboronic acid was chosen as the model reaction. First, the reaction conditions were optimized using different bases, solvents, and catalysts. Then, the impact of the initial concentration of each reactant on the reaction rate was determined, as well as the temperature effect. Finally, a simple model is proposed to take into account the experimental observations.

2. Results

2.1. Experimental Kinetic Study

2.1.1. Preliminary Observations

Among the four palladium complexes and the seven bases screened (Supplementary Materials Figures S1 and S2, Table S1), the Herrmann–Beller palladacycle (HB palladacycle) and sodium methylate were selected for this kinetic study. To briefly summarize this choice, the HB palladacycle displayed a negligible deactivation during the course of the experiments and it revealed the most active and selective catalyst for the SM coupling. Palladacycles were proposed as efficient catalysts for the cross-coupling between aryl halides and arylboronic acids by Beller et al. [25]. Sodium methylate allowed a complete solubilization of all reagents and products in ethanol even at room temperature. No micromixing issue resulted from the combined use of toluene and ethanol solutions (see details in Supplementary Materials Figures S3 and S4). The reaction can thus be described by Scheme 1.

Scheme 1. Suzuki–Miyaura coupling of 4-iodoacetophenone and phenylboronic acid.

2.1.2. Temperature Effect and Activation Energy

The effect of temperature on the SM reaction was studied by varying the temperature from 16 to 80 °C at a palladium concentration of 5·10⁻⁶ mol/L, with the other reaction parameters being kept constant. As expected, a temperature increase increased the reaction rate, for both concentrations of Pd.
The catalyst activity reached 175,000 h\(^{-1}\) at 80°C. The Arrhenius plot (Figure 1) gave an average value of 63 kJ/mol with a high standard deviation of 11 kJ/mol and a confidence coefficient of only 0.88.

![Figure 1](image1.png)

**Figure 1.** Arrhenius plot of Suzuki coupling of 4-iodoacetophenone and phenylboronic acid. The initial rates are normalized by the mass of Pd. Conditions: 4-iodoacetophenone (0.05 mol/L, 1 eq.), phenylboronic acid (0.06 mol/L, 1.2 eq.), MeONa (0.075 mol/L, 1.5 eq.), Pd (5 \(\times\) 10\(^{-6}\) mol/L), and ethanol (20 mL).

### 2.1.3. Effect of the Catalyst Concentration

The concentration of palladium was varied between 5 \(\times\) 10\(^{-6}\) and 5 \(\times\) 10\(^{-4}\) mol/L, but only the experiments with Pd concentrations lower than 2.2 \(\times\) 10\(^{-5}\) mol/L were used for the determination of the initial rate of the reaction because for higher Pd concentrations the reaction is so fast that initial rates cannot be determined. The initial reaction rate is first order with respect to initial Pd concentration (Figure 2). This first order can be explained by an instantaneous and non-rate-limiting transformation of the dimeric Pd precursor into monomeric Pd species.

![Figure 2](image2.png)

**Figure 2.** Effect of the initial concentration of Pd on the initial reaction rate. Conditions: 4-iodoacetophenone (0.05 mol/L, 1 eq.), phenylboronic acid (0.06 mol/L, 1.2 eq.), MeONa (0.075 mol/L, 1.5 eq.), Pd from 5 \(\times\) 10\(^{-6}\) to 2.2 \(\times\) 10\(^{-5}\) mol/L, ethanol (20 mL), and 60 °C.

### 2.1.4. Effect of the Aryl Halide Concentration

The aryl halide plays an important role in the oxidative addition elementary step, producing Pd(II) complex from Pd(0). This Pd(0)/Pd(II) mechanism was largely studied in the literature [26–28], and it is known to be a very fast step in SM reaction [16,17]. In order to determine the effect of aryl
halide concentration, the initial concentration of 4-iodoacetophenone was varied between 25 mmol/L and 100 mmol/L (Figure 3). The initial rates increase linearly with the concentration which indicates an apparent first order with respect to 4-iodoacetophenone.

\[
\text{Normalized initial rate} = 16699 \times [\text{ArI}]_0
\]

Figure 3. Effect of the initial concentration of 4-iodoacetophenone on the initial reaction rate. The initial rates are normalized by the mass of Pd. Conditions: 4-iodoacetophenone from 0.025 to 0.10 mol/L, phenylboronic acid (0.06 mol/L), MeONa (0.075 mol/L), Pd (5.10^{-6} mol/L), and ethanol (20 mL), 60 °C.

2.1.5. Effect of Base and Phenylboronic Acid Concentrations

Varying the concentration of phenylboronic acid from 0.03 to 0.15 mol/L or that of the base from 0.035 to 0.15 mol/L had no effect on the initial rate, as clearly shown in Figure 4.

Figure 4. Effect of the initial concentration of sodium methylate and phenylboronic acid on the reaction rate. The initial rates (logarithmic plot) are normalized by the mass of Pd. Conditions: 4-iodoacetophenone (0.05 mol/L), phenylboronic acid (from 0.03 to 0.15 mol/L), MeONa (from 0.035 to 0.15 mol/L), Pd (5·10^{-6} mol/L), ethanol (20 mL), and 60 °C.

2.2. Modeling and Discussion

Considering the textbook reaction mechanism [7], the fact that the reaction is first order toward ArI and Pd and zero order towards the other reactants is in favor of the oxidative addition being the rate-determining step. As a preliminary rapid transformation, it is expected that the palladacycle is fully transformed to Pd^{0} species. Then,
The following rate law was considered,

$$ r = k_0 e^{-\frac{E_a}{RT}} [\text{ArI}][\text{Pd}] $$

with $r$ being the rate of product formation (or that of ArI transformation). The experimental data points of the concentrations of both ArI and product were fitted using Equation (2) with the version 4.27 of COPASI (COmplex PAthway SImulator), available at http://copasi.org/ [29], taking into account the temperature as a “modifier”. The equation was solved using the genetic algorithm; the objective function being a weighted sum of squares (mean square weight). Using 23 experiments performed in batch and two experiments in the flow tube (seven flow rates per experiment), a total of 191 data points at conversion of the default reactant $<95\%$ was used to estimate $k_0$. With the value of $k_0 = (1.1 \pm 0.3) \cdot 10^{14}$ L/mol/min and $E_a = 63 \pm 1$ kJ/mol, the parity plot provided in Figure 5 is obtained, demonstrating that a good description of the kinetics can be simply made using a first-order law towards ArI and Pd. Note that data at various temperatures and at other Pd concentration than in Figure 1 were also used in the model and allowed to narrow the standard deviation. A good accordance with the mean value obtained from the initial rates is nevertheless obtained.

It is thus proposed that the oxidative addition is the rate determining step, in agreement with a recent study using a water-soluble Pd-\(\beta\)-cyclodextrin catalyst [24]. Other studies conclude that the rate-determining step is the trans-metallation [30] in the case of a ligand-free catalytic system, proving that the nature of the catalyst and the range of operating conditions can lead to different situations. The activation energy is similar to that obtained from initial rates. This value is in the range of what was published, as depicted in the introductory section [23,24,26].

3. Materials and Methods

The experiments were carried out in anhydrous ethanol (CARLO ERBA). The reagents 4-iodoacetophenone (Acros Organics, Geel, Belgium), and phenylboronic acid (Acros Organics); the bases MeONa, NaOH, CH$_3$COONa, NEt$_3$, K$_2$CO$_3$, K$_3$PO$_4$, and K$_2$HPO$_4$ (Sigma-Aldrich, St. Louis, MO, USA); and the solvents were used as received, without purification. Four homogeneous
palladium complexes (Sigma-Aldrich) were used: Herrmann–Beller palladacycle, PEPPSI-IPr catalyst, 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate, and Salicylaldehyde thiosemicarbazone palladium(II) chloride (ESI, Figure S1).

GC-FID chromatography (Agilent Technologies 6890N, column OPTIMA 5 (10 m × 100 µm × 0.1 µm), Split 1/250 volume injected 1 µL (300 °C), Flow H₂: 0.4 mL/min, Oven program: 150 °C (30 s) then 50 °C/min up to 340 °C (42 s), FID Detector). N-tetradecane (Acros Organics) was used as an internal standard.

Typical procedure for batch experiments: 4-iodoacetophenone (0.25 g, 1.0 mmol), phenyl boronic acid (0.15 g, 1.2 mmol), sodium methoxide (0.080 g, 1.5 mmol), n-tetradecane (0.08 g, 0.40 mmol) as a GC internal standard, and anhydrous ethanol (20 mL) were added to a three-neck round-bottom flask equipped with a stirring bar. The dissolution was improved using an ultrasonic bath at room temperature (Elmasonic S30H) for 30 min, after which time the flask was preheated at 60 °C inside an oil bath under agitation for 30 min. When this temperature was reached, a blank sample of 0.5 mL was syringed out for GC analysis and an aliquot (0.20 mL, 0.094 mg catalyst, 0.00020 mmolPd) of a Herrmann–Beller palladacycle toluene solution prepared separately (4.7 mg, 0.010 mmolPd in 20 mL toluene) was added. Samples were withdrawn periodically (0, 1, 2, 3, 5, 7, 10, 15, 20, 30, 40, 50, 60 min) during the course of the reaction. Immediately after sampling, all samples were quenched in a mixture of deionized water (2 mL) and dichloromethane (VWR) (1 mL). The heavier organic phase was collected, dried over MgSO₄, filtered through cotton wool, and analyzed using GC-FID.

Typical experiment in flow reactor: A solution was prepared by dissolution of 4-iodoacetophenone (2.5 g, 0.010 mol, 1.0 eq.), phenylboronic acid (1.5 g, 0.012 mole, 1.2 eq.), MeONa (0.81 g, 0.015 mole, 1.5 eq.), and n-dodecane (0.5 g, 0.003 mole, 0.3 eq.) in ethanol (400 mL). An ultrasonic bath (Elmasonic S30H) was used to help dissolution of all the reactants (ultrasound for 30 min at room temperature). Another solution was prepared by dissolution of the Herrmann–Beller palladacycle (I) (4.7 mg, 0.010 mmolPd) in 20 mL of toluene (VWR). The reagent solution was pumped (Shimadzu LC-20AP), and the catalyst solution was added (Programmable Syringe Pump Harvard PHD 4400 Hpsi) through the preheated (60 °C ± 2 °C) empty stainless steel tube (8.8 mm i.d SWAGELOK fittings); both solutions were mixed with a micromixer (SSIMM-IMM) or a T mixer (SWAGELOK) (Figure 6). Note that the residence time could be controlled both by the flow rate and the reactor length.

![Flow test experimental set-up.](image)

Initial rates were evaluated using different mathematical laws (polynomial and exponential), as explained in Supplementary Material Figure S5. A mean value was obtained from the different methods, as well as a standard deviation.

4. Conclusions

In this article, the experimental conditions of Suzuki–Miyaura reaction of 4-iodoacetophenone with phenylboronic acid have been optimized to avoid all mass transfer limitations, by initially choosing a stable active and selective homogeneous catalyst. Then, from a variety of bases, sodium
methyleate has been selected for its activity and solubility in ethanol. Furthermore, a kinetic study was carried out in two different reactors, batch and flow, by initially checking the effect of the initial concentration of each reactant on the initial reaction rate. In fact a quasi-first order was found for the 4-iodoacetophenone with a first order dependence on the initial concentration of palladium. A zero order was found for the other compounds, in accordance with the oxidative addition being the rate-determining step.

A global activation energy, with an average value of ca. 63 kJ/mol was determined. This study, restricted to an iodo derivative, needs to be extended. Future works, with the bromide and the chloride derivatives, and also with weaker bases, will shed more light in order to define their effects on the rate limiting step, the nature of the mechanism, and the form of the kinetic rate law.

**Supplementary Materials:** The following are available at http://www.mdpi.com/2073-4344/10/9/989/S1, Figure S1: List of the tested homogeneous catalysts, Figure S2: Choice of the base, Figure S3: Effect of palladacycle pre-dissolution in toluene, Figure S4: Verification that the reaction is not limited by micro-mixing or mass transfer, Figure S5: Method of initial rate determination, Table S1: Catalyst selection for the Suzuki-Miyaura coupling of 4-iodoacetophenone with phenylboronic acid.

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**Conflicts of Interest:** The authors declare no conflict of interest.

**Abbreviations**
The following abbreviations are used in this manuscript.

| Abbreviation | Description |
|--------------|-------------|
| SM           | Suzuki-Miyaura |
| ArI          | 4-iodoacetophenone |
| [Pd]         | Concentration of mononuclear palladium |
| Ea           | activation energy |
| r            | rate of product formation (mol/min) |

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