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Study on the Effect of the Ligand Structure in Palladium Organometallic Catalysts in the Suzuki-Miyaura Cross-Coupling Reaction †

Paula Munín-Cruz *, M. Rúa-Sueiro, J. M. Ortigueira, M. T. Pereira and J. M. Vila

University of Santiago de Compostela, Avd. das Ciencias s/n, Santiago de Compostela, Spain
* Correspondence: paula.munin@usc.es

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Abstract: In this communication, we present the results obtained using a family of cyclometallated palladium compounds as catalysts for the Suzuki-Miyaura cross-coupling reaction between an aryl halide and phenylboronic acid. We have studied the structural factors that enhance the efficiency of the catalyst for this process through the synthesis of a library of analogous compounds containing thiosemicarbazone ligands with substituted rings and ferrocene diphosphine (dppf). We found that the best conversion rates are obtained with ligands bearing methoxy-disubstituted aromatic rings; and that the process performance is improved when R^2 is a methyl group bound to the thioamidic nitrogen. These results lay the foundations for the design and development of novel and more efficient palladium catalysts based on thiosemicarbazones.

Keywords: organometallic chemistry; cyclometallation; catalysis

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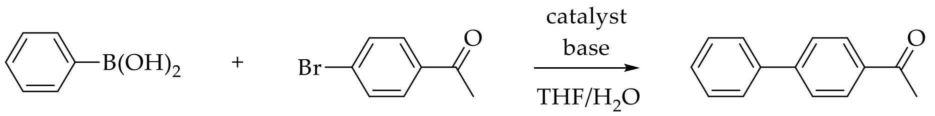
1. Introduction

The Suzuki-Miyaura cross-coupling describes the formation of a carbon-carbon bond between an organoborane and an alkenyl, aryl, or alkyl triflate or halide in the presence of base and a catalyst [1].

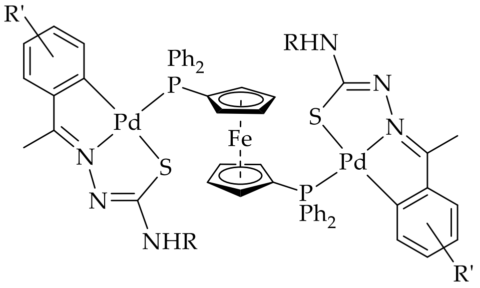
In this work, 4-bromoacetophenone and phenylboronic acid were chosen as the starting substrates, in the presence of a base and the appropriate amount of catalyst, using a mixture of THF and water as the solvent. The general catalytic process is shown in Scheme 1.



Scheme 1. General scheme of the catalytic process.

2. Materials and Methods

A family of cyclometalsated palladium compounds, capable of providing high catalytic activity due to their characteristics, has been synthesized [2–4]. Scheme 2 shows the general body that corresponds to the synthesized compounds. All of them have been characterized by ^1H and ^{31}P NMR spectroscopic techniques. Since these catalysts bear labile coordination ligands, such as diphosphine 1,1′-bis(diphenylphosphino)ferrocene (dppf), they are easily released and also stable in solution, which allows them to be regenerated.



1-22

Scheme 2. General structure of the catalysts.

We have already described the synthesis of these compounds in previous works [5]. In this work, we have evaluated the catalytic capacity of a total of 22 compounds. Table 1 shows the different substituents for each of the compounds.

Table 1. Summary of the substituents of the catalysts.

Catalyst Number	Substituent R′	[1] Substituent R
1	4-Br	H
2	4-Br	Me
3	4-Br	Et
4	4-OMe	H
5	4-OMe	Me
6	4-OMe	Et
7	3-OMe	H
8	3-OMe	Me
9	3-OMe	Et
10	3-OMe	Ph
11	3,4-OMe	H
12	3,4-OMe	Me
13	3,4-OMe	Et
14	3,4-OMe	Ph
15	2,4-OMe	H
16	2,4-OMe	Me
17	2,4-OMe	Et
18	2,4-OMe	Ph
19	2,3,4-OMe	H
20	2,3,4-OMe	Me
21	2,3,4-OMe	Et
22	2,3,4-OMe	Ph

[1] Compounds in which R′ = 4-Br or 4-OMe and R = Ph could not be synthesized.

The conditions used for the evaluation of the catalytic activity of catalysts **1-22** in the Suzuki-Miyaura reaction were the following: In a Radleys carousel tube, 20 mg of 4-bromoacetophenone and 14.7 mg of phenylboronic acid (1.2 eq) were added to a mixture of THF/H_2O (2:1). Then, 27.8 mg of potassium carbonate and the appropriate amount of catalyst (4 mol% in Pd) were added to the mixture, which was stirred at 80 °C for 24 h.

After 24 h, 0.1 mL of hydrochloric acid (0.1 M) were added and the mixture extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to remove the solvent.

The sample was then dissolved in $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy. The conversion rate is obtained by comparison of the integrals of the signals corresponding to the methyl groups of the reagent and the coupled product. An example is shown in Figure 1.

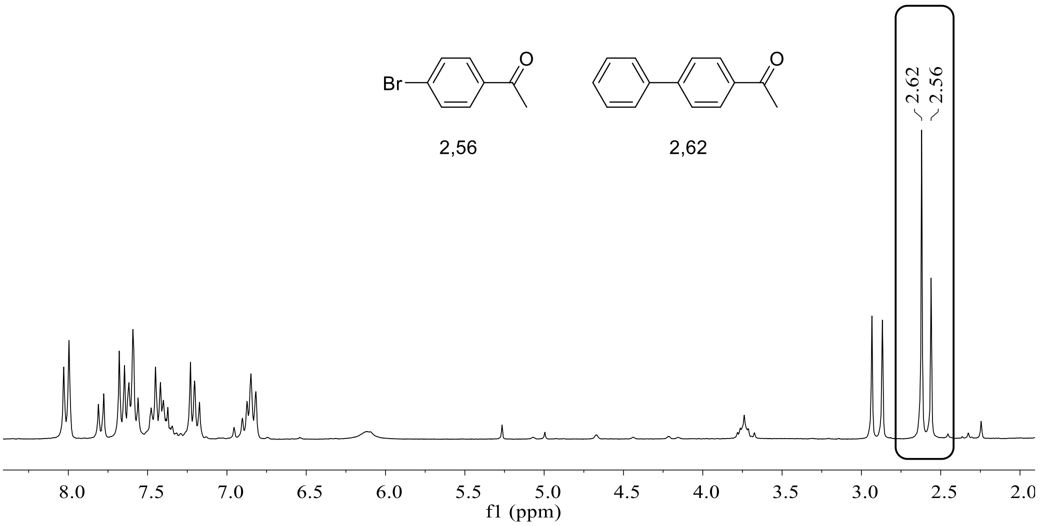


Figure 1. ^{1}H NMR spectra in CDCl$_3$ of the results obtained using catalyst **10**.

3. Results

The results obtained for the conversion using the thiosemicarbazone-based catalysts (**1-22**) are shown in Figure 2. As can be seen, the conversion rates vary according to the substituents R and R′. Five values higher than 60% were obtained, two of which were found to be higher than 80%.

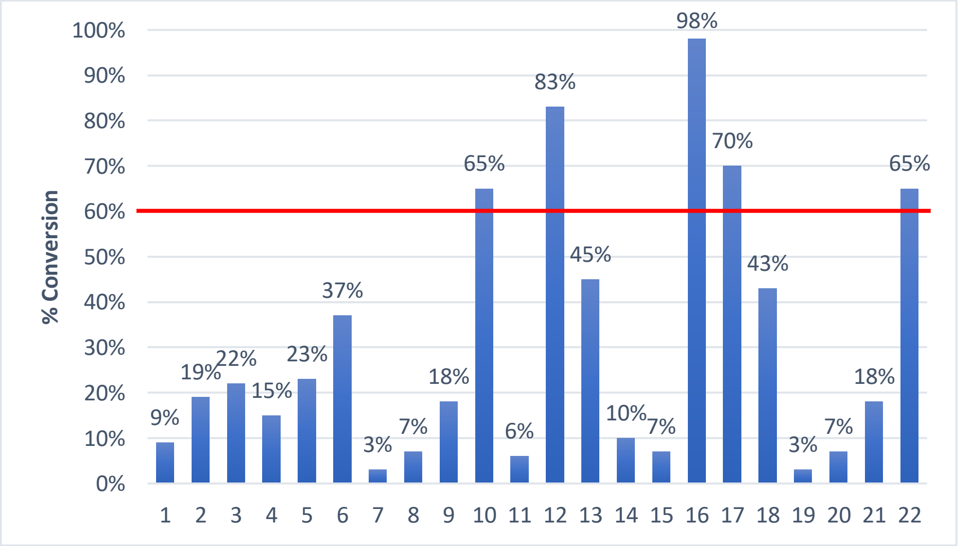


Figure 2. Summary of the conversion rate obtained with each catalyst.

4. Discusion

The results indicate that the best conversion rate is obtained using compound **16** as the catalyst (98%), followed by **12** (83%). Both compounds have in common two aromatic rings substituted by a methoxy group and a methyl group at the thioamidic position.

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