Artigo

EFFECTS OF SOLVENT, BASE, AND TEMPERATURE IN THE OPTIMISATION OF A NEW CATALYTIC SYSTEM FOR SONOGASHIRA CROSS-COUPLING USING NCP PINCER PALLADACYCLE

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The optimisation of a new catalyst system using NCP pincer palladacycle **1** was investigated using the experimental design technique. NCP pincer palladacycle **1** was previously investigated in Suzuki-Miyaura and Heck-Mizoroki cross-couplings and found to be a highly efficient catalyst precursor. In this study, the effects of the type of base (K_3PO_4 or DABCO), solvent (DMF or dioxane) and reaction temperature (130 or 150 °C) in the second step on the reactional yield in Sonogashira cross-coupling were assessed using the two-factor design. The results showed that temperature is statistically significant in relation to the reaction yield.

Keywords: Sonogashira cross-coupling; Dupont's catalyst; experimental design.

INTRODUCTION

Sonogashira cross-coupling is an important C-C reaction between aryl- or vinyl halides and terminal acetylenes.[1] The products of this reaction are key intermediates in the organic synthesis of natural products, pharmaceuticals and organic materials.[2] In most cases, the classical experimental protocol involves using a palladium source such as $[PdCl_2(PPh_3)_2]$ or $[Pd(PPh_3)_4]$ in the presence of Cu salts (Scheme 1).[3]

$$R-X \ + \ H-\!\!\equiv\!\!-R' \quad \xrightarrow[\text{base, solvent}]{[Pd] \ / \ Cu(I)} \quad R-\!\!\equiv\!\!-R'$$
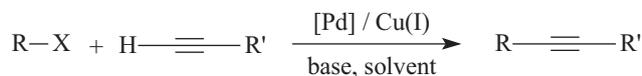
Scheme 1. Sonogashira cross-coupling

However, these traditional catalytic systems use large amounts of palladium (~ 5 mol%) and copper salts (~ 10 mol%), which prevent practical applications because of the difficulty of decontamination of the products and the high cost of the catalyst. Furthermore, the observed reactivity is of the following order: vinyl triflate ~ vinyl iodide > vinyl bromide > vinyl chloride > aryl iodide >> aryl bromide >> aryl chloride. Therefore, catalytic systems that promote the Sonogashira reaction with aryl chlorides are rare and fairly desired. More recently, copper-free catalytic systems promoted by palladacycles[4] and efficient coupling of aryl chlorides even in aqueous media have been reported.[5] Among these palladium sources, palladacycles have emerged as favourites particularly because of their unique properties, which include their facile synthesis, thermal stability and the possibility to readily modulate their steric- and electronic properties.[6] They have CP, CN, CS, PCP, SCS, NCN and NCP types in their molecular structures, and they can have rings with 5 and 6 members.[7] Our group has worked with NCP pincer palladacycle **1** and mentioned how Dupont's catalyst (Figure 1),[8] which is a phosphinite palladacycle with an aliphatic backbone that can perform the cross-coupling of aryl chlorides with arylboronic acids (Suzuki-Miyaura reaction) or with n-butyl acrylates (Heck-Mizoroki reaction), results in notably good to excellent yields.[7,9,10]
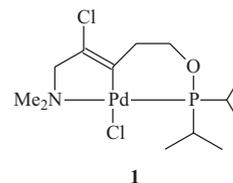

Figure 1. NCP pincer palladacycle (Dupont's catalyst)

However, the applicability of **1** in Sonogashira cross-coupling had not been tested. To develop a copper-free catalytic system, we attempted to use an experimental design tool.

The factorial design is a useful analytical strategy, whose main application is the screening of relevant variables of a given system.[11] After this screening process of the most significant variables, experiments are performed to allow refinement and a better understanding of the system under study.[12] Thus, the tool can be adapted to develop a catalytic system.

The present work aimed at studying and evaluating the effects of the base type (DABCO (1,4-diazabicyclo[2.2.2]octane) or K_3PO_4), type of solvent (DMF (N,N-dimethylformamide) or dioxane) and the reaction temperature (130 or 150 °C) on the Sonogashira cross-coupling yield.

EXPERIMENTAL

Experimental details

All reactions were performed in an argon atmosphere in an oven-dried resealable Schlenk tube. All substrates, which included K_3PO_4, DABCO and DMF, were purchased from Acros. 1,4-Dioxane was purchased from Synth. The chemicals were used without further purification. The mass spectra were obtained using a GC/MS Shimadzu QP-5050 (EI, 70 eV). The gas chromatography analyses were performed using a Hewlett-Packard-5890 GC with an FID and 30 m capillary column with a dimethylpolysiloxane stationary phase. Palladacycle **1** was prepared as described in an early study.[7]
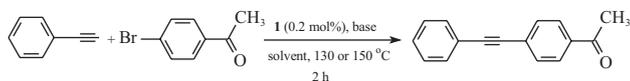
Typical experiment for Sonogashira cross-coupling

An oven-dried resealable Schlenk flask was evacuated and back-filled with argon and charged with dried base (0.35 mmol),

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4-bromoacetophenone (50 mg, 0.25 mmol), phenylacetylene (31 mg, 0.3 mmol) and NCP pincer **1** (0.2 mg, 5 × 10⁻⁴ mmol). The flask was evacuated and back-filled with argon, and 2 mL of solvent was subsequently added. The reaction mixture was stirred at 130 °C or 150 °C for 2 h (Scheme 2). The product was identified using GC/MS. The GC yield was taken as the average of two runs.
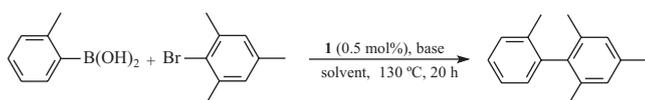

Scheme 2. *Sonogashira cross-coupling of phenylacetylene with 4-bromoacetophenone catalysed with* **1**

4-MeCOC₆H₄C≡CPh. GC-MS (IE, 70 eV) m/z (%): 220 (M⁺, 3), 205 (M⁺-Me, 23), 176 (38), 163 (5), 151 (15), 87 (26).

Typical experiment for Suzuki-Miyaura cross-coupling

An oven-dried resealable Schlenk flask was evacuated and back-filled with argon and charged with dried base (0.5 mmol), 2-bromomesitylene (50 mg, 0.25 mmol), 2-tolylboronic acid (51 mg, 0.37 mmol) and NCP pincer **1** (5 mg, 1.25 × 10⁻³ mmol). The flask was evacuated and back-filled with argon, and 2 mL of solvent was subsequently added. The reaction mixture was stirred at 130 °C for 20 h (Scheme 3). The product was identified using GC/MS. The GC yield was taken as the average of two runs.

Scheme 3. *Suzuki-Miyaura cross-coupling of 2-tolylboronic acid with 2-bromomesitylene catalysed with* **1**

2,2',4,6-Tetramethylbiphenyl. GC-MS (IE, 70 eV) m/Z: 210 (M⁺), 195, 180, 179, 165, 152, 141, 128.

Experimental design in Sonogashira cross-coupling reaction

The experimental design is a tool that is used in many analysis processes, new formulations of systems operations and improvement of usual operation systems. The experimental design allows one to study the effects and relationship between one or more responses (output variable) and a set of factors (input variables), which are obtained as one of the advantages to reduce the number of tests. The yield of the Sonogashira cross-coupling reaction was evaluated according to the effect of the following variables: A) temperature, B) solvent, and C) base; their respective levels of variation are shown in Table 1. A full factorial 2^3 experimental design was used.

Table 2 shows the array of the full factorial 2^3 experimental design.

The results obtained during step 2^3 of the experimental array, which is obtained from an empirical statistical model, are used to predict the response variable in the studied process. The response

Table 1. Factors and levels studied in the Sonogashira cross-coupling reaction, which was catalysed with **1**, in the experimental design

	Coded Levels	
	-1	+1
Temperature (°C)	130	150
Solvent	Dioxane	DMF
Base	K_3PO_4	DABCO

Table 2. 2^3 full factorial design matrix

Essays	Factors		
	Temperature (°C)	Solvent	Base
1	-1	-1	-1
2	+1	-1	-1
3	-1	+1	-1
4	+1	+1	-1
5	-1	-1	+1
6	+1	-1	+1
7	-1	+1	+1
8	+1	+1	+1

variable is the reactional yield (%), which is considered a random variable y and distributed around a population average $\eta(x_1,x_2)$ with a population variance $\sigma^2(x_1,x_2)$ (Equation 1):

$$y(x_1,x_2) = \eta(x_1,x_2) + \varepsilon(x_1,x_2) \qquad (1)$$

where ε is the fluctuation around the middle values.

For this statistical test, the model with only the main effects is used. Additionally, it was assumed that the deviations vary according to a normal distribution, i.e., for the full factorial planning, the average population $\eta(x_1,x_2)$ can be represented by a linear combination of the variables x_1 and x_2 (Equation 2):

$$\eta(x_1,x_2) = \beta_0 + + \beta_1 x_1 + + \beta_2 x_2 \qquad (2)$$

or through Equation 3:

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \varepsilon \qquad (3)$$

where β_0 is the global average value of responses, and β_1 and β_2 are the population values of the linear effects of the main effects and the effect of the interaction per unit of x_1 and x_2.

The statistical models that are tested to adjust the experimentally obtained values are evaluated according to the analysis of variance and coefficient of determination. Additionally, the location of levels of x_1, x_2, ...,x_k that maximise the estimated response (predicted) is held. If this point exists, it is a set of x_1, x_2, ...,x_k for which the partial derivatives are zero (Equation 4):

$$\partial \hat{y} / \partial x_1 = \partial \hat{y} / \partial x_2 = ... = \partial \hat{y} / \partial x_k = 0. \qquad (4)$$

After the statistical analysis of coefficients, the effect of the factors and their interactions on the responses is analysed using the analysis of variance (ANOVA) and coefficient of determination (R²) to verify whether the model represents a degree of fit for the experimental data. These models were evaluated using the software *Statistica* 6.0®.

RESULTS AND DISCUSSION

A full 2^3 factorial planning was used to evaluate the effect of the following variables: A) Temperature (°C), B) Solvent, and C) Base with predefined coded levels on the percentage of Sonogashira cross-coupling yield. Table 3 shows the array of the complete planning and the 2^3 answers that were obtained for each test.

With the obtained results in Table 3, the effects of these three independent variables on the experimentally obtained responses

Table 3. 2³ experimental design matrix with the respective answers

Entry	Factors			Response Yield (%)
	Temperature (ºC)	Solvent	Base	
1	-1	-1	-1	0
2	+1	-1	-1	30
3	-1	+1	-1	42
4	+1	+1	-1	12
5	-1	-1	+1	8
6	+1	-1	+1	33
7	-1	+1	+1	41
8	+1	+1	+1	5

and their respective statistical indices were analysed, as shown in Table 4.

In Table 4, note that the temperature effect is statistically significant for the level of confidence of 95% because the confidence interval (-95% to +95% confidence limit) does not contain the number zero, which indicates that the factor under consideration does not provide a null effect, i.e., the tested confidence level is not considered to be significant. Additionally, a coefficient of determination (R^2) of 0.9929 was obtained.

The algebraic sign of the observed effects is consistent with the knowledge of the phenomena involved. Because an increase in temperature leads to a higher percentage of income of the coupling reaction, the temperature is directly proportional with the yield. In addition, similar behaviours were observed for the calculated effects of the solvent factor (3.750) and base (0.750).

Figures 2 and 3 show the contours that correspond to the response surface, which was generated using the empirical model for the temperature, solvent and base for a yield percent response of the reaction.

Figures 2 and 3 show that with the variation in temperature of the reaction system, the percentage yield of the reaction sharply varies. In addition, the biggest reaction yields are obtained in the optimum region of 143-152 ºC (levels 0.3-1.2). For the tested bases and solvents, the system behaviour was hardly affected, and the base DABCO can be attached to the solvent DMF. In the empirical model for the percentage of income of the Sonogashira cross-coupling reaction, the studied levels are represented by Equation 5.
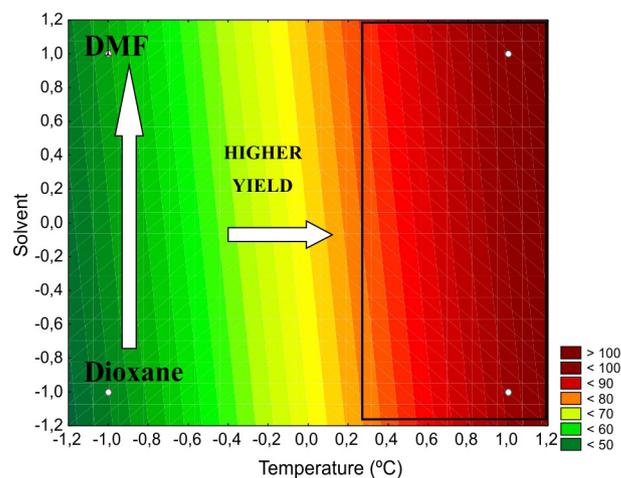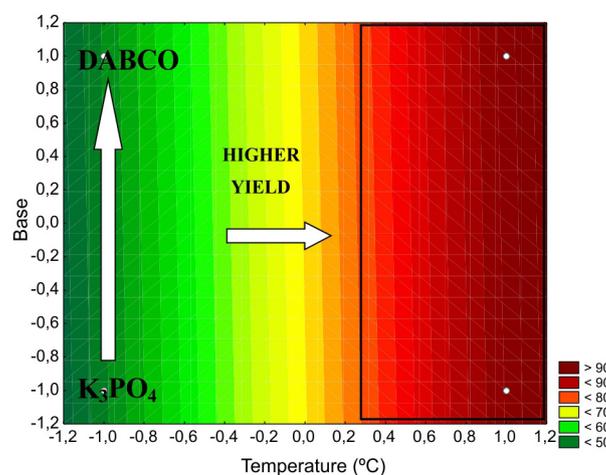
$$Y = 74.12 + 22.37\ T \tag{5}$$

where Y is the yield of the reaction in percent (%), and T is the temperature of the reactional medium in ºC.

The analysis of variance (ANOVA) shows that the value of the calculated F distribution (416.11) for the waste is related to regression, and the F distribution list is shown (5.9874 for 1 degree of freedom and 6 for 2 degrees of freedom). Thus, the decline is significant and can be used for prediction purposes. Additionally, the coefficient of determination (R^2) of 0.9858 was obtained. All statistical indices show that the fitted model (Equation 5) describes well the experimental results.
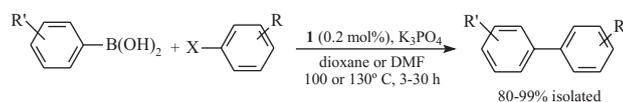

Figure 2. *Contours to the solvent and temperature factors*

Figure 3. *Contours to the base and temperature factors*

This result is contradictory to that of previous study for the Heck-Mizoroki coupling (Scheme 4).[10] The reaction of 4-bromoanisole with *n*-butyl acrylate, which is catalysed by **1** with DABCO as the base and DMF as the solvent, gives the worst results. However, the effect on the reaction yield in both base and solvent is low.
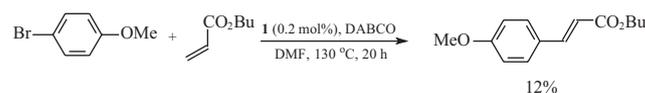
Scheme 4. *Heck-Mizoroki cross-coupling catalysed with **1***

K_3PO_4 (base) was evaluated for the Suzuki-Miyaura cross-coupling of different aryl halides with arylboronic acids that was catalysed with **1** (Scheme 5). Surprisingly, the base produced excellent yields in both reactions using DMF and using dioxane.[7]

Additionally, a negative effect on the response performance was identified in another Suzuki-Miyaura cross-coupling investigation

Table 4. Calculations of the effects and their statistical indices regarding to the percentage yield of Sonagashira cross-coupling

	Effect	Standard Deviation	Test t *Student*	Level p	-95% Confidence limit	+95% Confidence limit
Average/Interactions	**74.125**	**0.944**	**78.545**	**0.000**	**71.505**	**76.745**
(A) Temperature (ºC)	**44.750**	**1.887**	**23.709**	**0.000**	**39.510**	**49.990**
(B) Solvent	3.750	1.887	1.987	0.118	-1.490	8.990
(C) Base	0.750	1.887	0.397	0.711	-4.490	5.990

Scheme 5. *Suzuki cross-coupling catalysed with* **1**

between 2-tolylboronic acid and 2-bromomesitylene using palladacycle **1** at constant temperature of 130 °C but with KF and CsF bases, which changed the solvent from dioxane to DMF with an 80% confidence. Thus, when the solvent is changed to DMF, the reaction yield is reduced, i.e., from 56 to 45% with KF and from 60 to 38% with CsF. The base change for CsF to KF showed results similar to those of dioxane, which is an adverse effect on the yield (Table 5).

Table 5. Main effects of the full factorial design 2^2 to Suzuki-Miyaura cross-coupling

		Main effects	p
Yield	Solvent*	-16.5	0.20
	Base	-1.5	0.83

*$p < 0,20$ (significant for an 80% confidence level).

For the reaction temperature, we evaluated the catalytic system activation in Suzuki-Miyaura coupling with DMF and K_3PO_4. It was found that **1** required temperatures above 80 °C for greater efficiency, and the optimum range was 100-130 °C. In the cross-coupling of 4-chlorophenylboronic acid and iodobenzene at 25 °C (room temperature), for a reaction time of 190 h, only 25% of the coupling product was obtained. When the catalyst concentration is increased by five times, the product concentration was only doubled (53%) under the identical reaction conditions, which correlates to the difficulty of palladacycle **1** in generating catalytically active Pd species at low temperatures. It is believed that the catalytically active species is the product of partial dechelation of NCP pincer **1**; however, further investigation must be performed for such information.[6] This fact also reinforces the positive response at high temperature (optimum region of 143-152 °C) of the Sonogashira cross-coupling.

CONCLUSIONS

In summary, the experimental design tool was used to evaluate the contribution of temperature, solvent and base in the development of a new catalytic system for Sonogashira cross-coupling using palladacycle **1**. This evaluation permits the construction of a statistically significant model with 95% (correlation factor of 0.99), which describes the reaction yield as a function of these variables. Differences were found for other catalyst systems that have been optimised for Heck-Mizoroki and Suzuki-Miyaura cross-couplings using the same catalyst precursor. Such differences reside in the electronic properties of the substrates (phenylacetylene, *n*-butyl acrylate and arylboronic acid) and the steps of the catalytic cycle. However, **1** deserves special attention because it is one of the few phosphine-free palladium sources that promote high yields for both Heck and Suzuki cross-coupling reactions with aryl chlorides. In this work, **1** shows great potential to

be applied in a copper-free catalytic system for Sonogashira cross-coupling of aryl bromides using low amounts of catalyst (0.2 mol%) in a short time (2 h). Our group continues working to enhance the catalytic system to be active with aryl chlorides and their applications in agrochemical fields.

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