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4′-Methylbiphenyl-2-carbonitrile synthesis by continuous flow Suzuki–Miyaura reaction

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ABSTRACT

In the present work we report a high selective synthesis of the bicyclic core present in an important angiotensin II inhibitor family of drugs (*Sartans*) under continuous flow conditions. The key step in our approach was a Suzuki–Miyaura coupling using for the first time the recently described 4-toluylboronic acid MIDA ester.

Introduction

The Suzuki–Miyaura reaction is the Pd-catalyzed reaction between organoboron compounds and an organic halide and is nowadays the most important approach to the synthesis of biaryls. These biaryl scaffolds find innumerous applications in the synthesis of natural products,[1] pharmaceutical intermediates,[2] pesticides,[3] and covalent organic frameworks (COFs).[4] This scenario was established due to the low toxicity of the organoboron compounds, the mild reaction conditions, the availability, and easy preparation of the organoboron coupling partner that are behind its high acceptance in the chemical synthetic community.[5]

Despite all these conveniences, a major challenge in these palladium catalyzed cross coupling reactions lies in separating the product from the catalyst and as a consequence its recovery when working on homogeneous systems, leaving the large scale production expensive and difficult. On the other hand, solid supported Pd catalysts have been developed for several cross-coupling reactions allowing the catalyst's recovery and recycle and enabling the production of palladium free products which avoids the need to purge the residual transition metal from the final active pharmaceutical ingredient (API) product.[6–10]

A review on cross coupling reactions under continuous flow protocol was published by Buchwald et al.[11] and shows that significant effort has been devoted to develop a wide variety of continuous flow techniques to facilitate organic synthesis. On the Suzuki–Miyaura reaction, a board range of solid supports were reported, such as, polymer beads, monolithic supports, silica, and PdEnCat™. In addition, when compared to homogeneous catalysts, heterogeneous catalytic systems present lower levels of residual metals on the final product and the reactions are usually performed in the absence of ligands such as organic phosphines.

For industrial purposes, continuous flow reactions are preferred to batch reactors due to their greater process control, high productivity, and improvement of quality/purity and yield.[11–13] Several types of reactors can be used in continuous operation, and among these, packed bed reactors (PBR) are the most popular due to their high efficiency, low cost, and ease of construction, operation, and maintenance.[14]

In the scope of the Suzuki–Miyaura cross-coupling reactions, the one involving 2-bromobenzonitriles (**1**) and 4-methylphenylboronic acid derivatives (**2**) is an important transformation in the context of the synthesis of pharmaceutical intermediates,[2] since the 4′-methylbiphenyl-2-carbonitrile (**3**) obtained is present in building blocks of the angiotensin II inhibitors for the treatment of hypertension known as the 'Sartan' family (**4**, Fig. 1).

Despite the simplicity of this transformation at first sight, there have been reports concerning many difficulties in this reaction. The major drawback reported is the hydrolysis to the corresponding amide and/or dehalogenation of the nitrile substrate.[2] These hydrolysis products require additional steps of purification which

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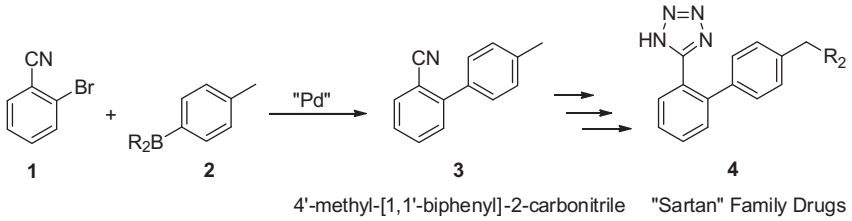


Figure 1. Building block of the 'Sartan' family.

are costly, lowering the chemical and economical efficiency of the reaction.

Results and discussion

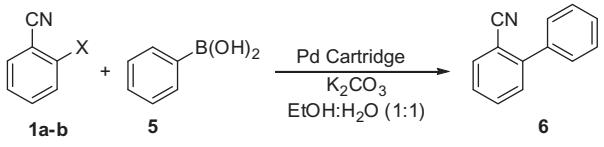
As a first step we have optimized the reaction parameters, that is, catalyst type, flow rate, and temperature in the reaction between 2-bromobenzonitrile (**1a**) and phenylboronic acid (**5**) as a model for our target and the results are shown in Table 1.

As it has been shown in Table 1, the FibreCat 1007, when compared with other catalysts, gave the cross-coupling product **6** in high yields. With this catalyst, on the reaction with 2-bromobenzonitrile (**1a**) as substrate, we can observe that higher residence time and higher temperatures can lead to a decrease in yield of the desired product, which is associated with an increase of the dehalogenated product (11%), entry 11. This behavior indicates a narrow temperature/flow rate window for optimization. The FibreCat 1007 catalyst was also essayed in the reaction between the less reactive 2-chlorobenzonitrile (**1b**) (entries 13–16) and phenylboronic acid (**5**). It can be observed the same influence of flow rate and temperature on the yields, however with a lower conversion. The selectivity is dropped with lower flow rates, in this case not only due to dehalogenation of the nitrile substrate but also by homocoupling reaction and protodeboration of starting materials.

With the temperature, catalyst, and flow set for the model reaction, the reaction was performed with the 4-toluylboronic acid MIDA ester (**7**) and 2-bromobenzonitrile (**1a**). The choice of working with the 4-toluylboronic acid MIDA ester (**7**) comes from the fact that this group is used for protection of the boronic acid functionality. The development of a cross coupling methodology under continuous flow conditions for these protected boronic acid derivatives is of great importance once it allows the functionalization of these derivatives without worrying with the boron Lewis acidity and the need for deprotection before the cross coupling reaction. We believe it is an important aspect for the development of boron based synthetic strategies such as those developed for the 'Sartan' family.

The results obtained by the use of the 4-toluylboronic acid MIDA ester (**7**) to the synthesis of intermediate **3**, is presented in Table 2.

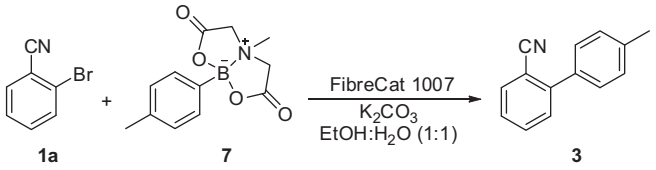
Table 1
Optimization of a Suzuki–Miyaura reaction between 2-halobenzonitrile and phenylboronic acid (**5**) under continuous flow



Entry	Catalyst	X	Temperature (°C)	Flow rate (mL/min)	Residence time (min)	6[a] (%)
1	FibreCat	Br	110	0.3	2	15
2	1001	(**1a**)		1.0	0.6	53
3			130	0.3	2	23
4				1.0	0.6	91
5	FibreCat	Br	110	0.3	2	41
6	X00017	(**1a**)		1.0	0.6	48
7			130	0.3	2	24
8				1.0	0.6	41
9	FibreCat	Br	110	0.3	2	98
10	1007	(**1a**)		1.0	0.6	97
11			130	0.3	2	73
12				1.0	0.6	99
13		Cl	130	0.2	3	53
14		(**1b**)		0.5	1.2	30
16				1.0	0.6	45

[a] Based on CG-MS analysis. Reaction conditions: 2-Halobenzonitrile (1.0 mmol), phenylboronic acid (**5**, 1.2 mmol), K_2CO_3 (1.2 mmol), ethanol/water (12.5 mL:12.5 mL).

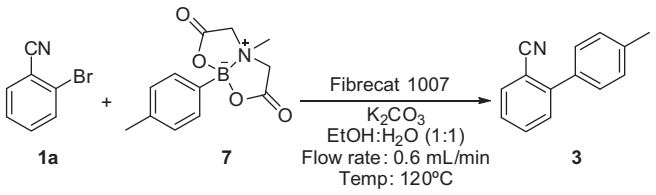
Table 2
Suzuki–Miyaura reaction between 2-bromobenzonitrile and 4-toluylboronic acid MIDA ester (**7**) under continuous flow



Entry	Catalyst	Temperature (°C)	Flow rate (mL/min)	Residence time (min)	3[a] (%)
1	FibreCat	110	0.3	2	25
2	1007	110	1.0	0.6	25
3		120	0.6	1	34
4		130	1.0	0.6	25

[a] Based on CG-MS analysis. Reaction conditions: 2-Bromobenzonitrile (**1**, 1.0 mmol), 4-toluylboronic acid MIDA ester (**7**, 1.2 mmol), K_2CO_3 (1.2 mmol), ethanol/water (12.5 mL:12.5 mL).

Table 3
Recycle continuous flow analysis

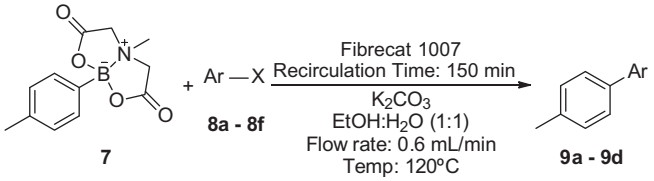


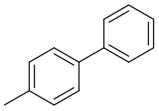
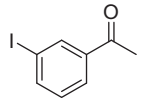
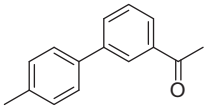
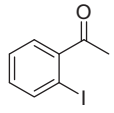
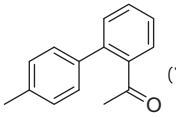
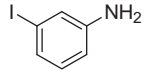
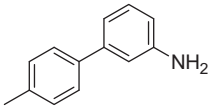
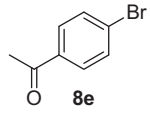
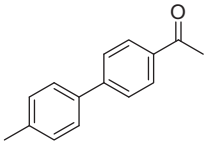
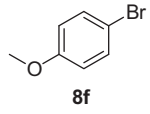
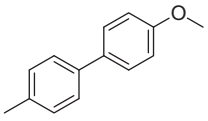
Entry	Catalyst	Recirculation time (min)	3[a,b] (%)
1	FibreCat 1007	30	12
2		60	28
3		90	37
4		120	47
5		150	54

[a] Based on CG-MS analysis; Reaction conditions: 2-Bromobenzonitrile (**1**, 1.0 mmol), 4-toluylboronic acid MIDA ester (**7**, 1.2 mmol), K_2CO_3 (1.2 mmol), ethanol/water (12.5 mL:12.5 mL).

[b] Isolated yields.

Table 4
Suzuki–Miyaura reaction between aryl halides and 4-toluylboronic acid MIDA ester (**7**) under continuous flow



Entry	Ar–X	**9a–9f**[a] (%)
1	 **8a**	 (63%) **9a**
2	 **8b**	 (86%) **9b**
3	 **8c**	 (74%) **9c**
4	 **8d**	 (38%) **9d**
5	 **8e**	 (56%) **9e**
6	 **8f**	 (15%) **9f**

[a] Based on CG-MS analysis. Reaction conditions: Aryl halides (0.5 mmol), 4-toluylboronic acid MIDA ester (**7**, 0.6 mmol), K_2CO_3 (0.6 mmol), ethanol/water (12.5 mL:12.5 mL).

It is important to note that to the best of our knowledge, this is the first study of the Suzuki reaction using boronic acid MIDA ester under continuous flow conditions. As can be seen the 4-toluylboronic acid MIDA ester (**7**) presents lower conversion than the phenylboronic acid (**5**). An attempt to increase the yield would be to increase the residence through lower flow rates. As we have already discussed in Tables 1 and 2, an increase in residence time leads to a decrease in selectivity which is mainly due to dehalogenation of the halonitrile partner, what prevented us from increasing the length of the catalyst bed or decrease the flow rate.

On the other hand, an increase in residence time could be achieved by recirculation of the solution through the cartridge, in a flow rate high enough to maintain the selectivity. We then performed a study under the best condition developed in Table 2 with different recirculation cycles and the results are presented in Table 3.

With this strategy a great improvement was observed on yield after 150 min of recirculating the reaction media, which was accompanied by a very small drop in selectivity, representing a very important aspect for further developments.

The success in the reaction depicted in Table 3 prompted us to evaluate the scope of the methodology developed, and the results are presented in Table 4.

As it can be seen in Table 4 the methodology developed for the cross coupling of 4-toluylboronic acid MIDA ester (**7**) with aryl halides (**8a–f**) under continuous flow conditions can be expanded on aryl iodides and bromines as long as these substrates do not carry electron releasing groups. These substrates lead to moderate and good yields as can be seen in entries 1–3 and 5.

Conclusion

In conclusion we report the development of the first methodology for cross coupling of 4-toluylboronic acid MIDA ester with aryl halides under continuous flow conditions. This methodology leads to a high selective synthesis of the bicyclic core present in the 'Sartan' drug family.

Acknowledgment

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