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Functionalization at the C3 position of the cephalosporin pharmacophore by palladium-catalyzed cross-coupling reactions[†]

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Herein, we describe a new methodology for selective cephalosporin functionalization at the C3 position. First, an optimization study of the reaction conditions was performed and allowed favourable parameters for the Suzuki–Miyaura coupling reaction to be defined. Then, the scope of the reaction was evaluated using various boronic acids, and the reaction demonstrated a good functional-group tolerance profile. Finally, the formation of some side-products was also investigated, and the main limitations of the reaction were defined.

1. Introduction

Since the discovery of penicillin G in 1928, structurally characterized by a β -lactam moiety, mankind has moved into the modern era of antibiotics. Subsequently, several other antibiotic families were developed around this crucial 4-membered ring, such as monobactam, carbapenem or cephalosporin.¹ Today, β -lactam agents account for more than 60% of prescribed antibiotics worldwide, profoundly impacting global human health.² However, this major milestone in modern medicine is being challenged by the emergence and spread of bacterial resistance, threatening the efficacy of the current antibiotic arsenal.^{3,4} To secure our future, it is necessary to explore new β -lactam analogues and consequently new methodologies are required to synthesize them. Among the various β -lactam families, cephalosporin represents the most extensively developed scaffold, with numerous marketed drugs, acting as antibacterial or adjuvant agents.⁵ The corresponding structure–activity relationships (SARs) are well-established and

all last-generation cephalosporins share common features, such as the oxime moiety to reduce β -lactamase recognition, and the amino-thiazole heterocycle for optimal penicillin-binding protein (PBP) inhibition profile (Fig. 1).⁶ The C3 position of the cephalosporin pharmacophore remains the last tunable site, with a wide variety of substituents already described. It is a crucial position to modulate several parameters, such as enzyme inhibition potency, aqueous solubility or even periplasm accumulation. A sp^2 – sp^2 bond on the C3 position is of great interest, as demonstrated by the marketed cefditoren and cefdinir (Fig. 1), ranked in the US Top300 prescription drugs.⁷

Nevertheless, the industrial synthetic pathways involved require harmful and environmentally costly reagents, offering limited opportunities for divergent synthesis approaches. The introduction of palladium-catalyzed coupling reactions has been a game-changer in the medicinal chemistry field.⁸ For the cephalosporin core, only Stille coupling reactions are described to decorate the C3 position. This methodology was successfully implemented in the synthesis of PBP and β -lactamase inhibitors.^{9–13} While it represents a viable and versatile approach, Stille coupling has some notable drawbacks, especially the acute toxicity of mandatory tin-based reagents. To overcome this limitation, we decided to explore the safer Suzuki–Miyaura coupling for C3 functionalization on the cephalosporin core. We recently published a similar approach for the synthesis of monobactam conjugates, based on Buchwald–Hartwig amination.¹⁴

2. Results and discussion

The cephalosporin triflate **1** was prepared from the corresponding commercially available enol, after optimization of the literature protocol, in a good yield (see ESI[†]). As a model substrate, we selected the 4-vinylphenylboronic acid **2a**. Firstly, we intended to develop a room temperature reaction to avoid

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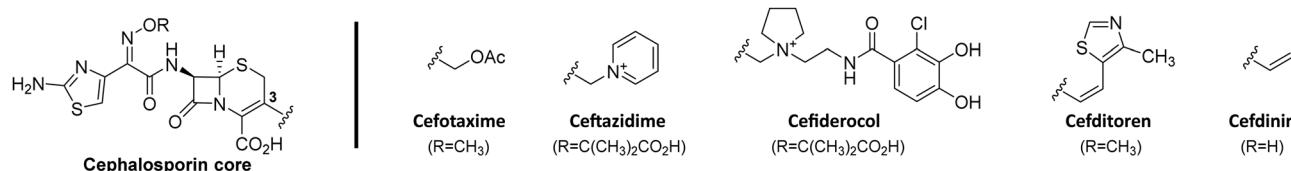


Fig. 1 Representative panel of marketed cephalosporin agents.

any side reactions, especially the well-known double bond Δ^3 - Δ^2 isomerization of the cephalosporin, and the protodeboronation phenomenon.^{15,16} The starting catalytic conditions were based on the standard palladium acetate-triphenylphosphine mixture using potassium carbonate as a base. All reactions were monitored by liquid chromatography-mass spectrometry (LC-MS) and reaction times were adjusted according to the observed conversion rate and are detailed in Table 1.

The influence of the solvent was preliminary investigated, and we firstly selected the two most common solvents, *i.e.* toluene and dioxane.¹⁷ In both cases, the starting cephalosporin **1** was degraded and only a small amount of the desired coupled cephalosporin **3a** was detected (Table 1, entries 1 and 2). The use of polar aprotic solvents, like acetonitrile or DMF, led only to rapid degradation of the starting material, without the formation of the desired compound (Table 1, entries 3 and 4). However, THF as the solvent demonstrated a better ability to perform the reaction, and after 24 hours at rt, a full conversion was reached. The reaction time can be efficiently reduced to 1 h under reflux conditions, without any side-product formation. In both cases, the isolated cephalosporin **3a** was obtained in a good yield (Table 1, entries 5 and 6). Sometimes, the addition of

a small amount of water in THF can improve the coupling kinetic reaction.¹⁸ In our case, the use of this mixture (Table 1, entry 7) led only to the degradation of the starting triflate **1**, with only traces of the desired compound **3a**. To provide a greener approach, 2-Me-THF was also investigated and led to clean conversion (Table 1, entry 8).^{19,20} Concomitantly, we also demonstrated that it was possible to reduce the catalytic charge (10 mol% of ligand, 5 mol% catalyst) leading to 55% yield (Table 1, entry 9). The palladium source can be divided between two parts, according to the oxidative state of the metal: Pd(II) or Pd(0). The Pd₂(dba)₃ complex was used as a stable Pd(0) source (Table 1, entry 10), instead of the regular Pd(II) acetate, but only a poor conversion rate was observed. This may demonstrate that the reduction step, to form *in situ* the Pd(0) entity, is not a limiting factor, or that the Pd₂(dba)₃ complex is too stable to proceed to the next oxidative addition step. Even though potassium carbonate is economically attractive, cesium carbonate has provided better reaction rates in numerous examples in the literature. In our case, this modification had a deleterious impact, with only a weak conversion rate (Table 1, entry 11). As the nature of the ligand used is often a key parameter in Pd-catalyzed coupling reactions, we also investigated this

Table 1 Reaction condition optimization of the Suzuki–Miyaura coupling^a

Entry	Precatalyst	Ligand	Base	Time (h)	Temperature	Solvent	Yield (conversion rate) ^b	
							3a	3a
1	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	1	rt	Toluene	(4%) ^c	
2	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	5	rt	Dioxane	(30%) ^c	
3	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	1	rt	CH ₃ CN	— ^f	
4	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	1	rt	DMF	— ^f	
5	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	24	rt	THF	64% (100%)	
6	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	1	65 °C	THF	70% (100%)	
7	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	1	rt	THF-H ₂ O	Trace ^d	
8	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	4	65 °C	2-Me-THF	58% (100%)	
9	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	1	65 °C	THF	55% (100%) ^e	
10	Pd ₂ (dba) ₃	PPh ₃	K ₂ CO ₃	5	rt	THF	Trace ^d	
11	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃	1	rt	THF	(23%) ^d	
12	Pd(OAc) ₂	JohnPhos	K ₂ CO ₃	1	rt	THF	— ^f	
13	Pd(OAc) ₂	XPhos	K ₂ CO ₃	1	rt	THF	(8%) ^d	
14	PEPPSI-iPr ^g		K ₂ CO ₃	24	rt	THF	— ^f	
15	XPhos-Pd G4 ^g		K ₂ CO ₃	2	rt	THF	— ^f	
16	XPhos-Pd G4 ^g		K ₂ CO ₃	5	65 °C	THF	55% (100%)	

^a DPM = diphenylmethyl, Ph₂CH. Reaction conditions: **1**, 0.16 mmol, 1 eq.; **2**, 1.2 eq.; precatalyst, 10%; ligand, 20%; base, 3 eq. solvent, 3.2 mL.

^b Isolated yield after column chromatography and conversion rate determined by LC-MS in brackets. ^c Not isolated. ^d Product only detected by LC-MS. ^e Precatalyst, 5%; ligand, 10%. ^f No product detected. ^g Palladium-ligand precatalyst at 10%.

parameter. Among the abundance of available ligands, we selected a panel of representative phosphines with different behaviors. The development of biaryl phosphanes provided numerous new insights into metal-catalyzed reactions and we choose JohnPhos and XPhos ligands, based on the distinct substituent size on the phenyl part.²¹ Sadly, neither biaryl phosphanes exhibited any significant catalytic activity (Table 1, entries 12 and 13). Finally, we explored “all-in-one” precatalysts with the electron-rich carbene PEPPSI-iPr and the *N*-substituted XPhos-Pd G4.^{22,23} No significant reaction occurred in these conditions at room temperature and a moderate yield was reached with XPhos-Pd G4 under reflux of THF for 5 h (Table 1, entries 14–16).

Once the best conditions were identified (Table 1, entry 6), the scope of the reaction was studied, with a focused library of eight boronic acids **2b–i**, variously substituted. Initially, we intended to introduce a phenyl group by using two boron-based reagents: the boronic acid **2b** and the corresponding pinacol ester (data not shown). Only the boronic acid reagent led to the desired 3-phenyl-cephalosporin **3b** in good yield (Table 2, entry 1) and no product was detected with the less reactive pinacol ester.²⁴ To further establish the functional-group tolerance of the coupling reaction, a boronic acid containing a diol (**2c**) was synthesized (see ESI,† for detailed protocols). Using this, no reaction was detected (Table 2, entry 2). As the corresponding protected acetal **2d** and the 6-membered acetal ring **2e** were also obtained as intermediates, they were also tested in this reaction. In both cases, full conversion into the corresponding cephalosporins was observed. Nevertheless, partial removal of the acetal protecting group occurred during the reaction, especially in the case of the 1,3-dioxane ring, leading to a complex reaction mixture. Consequently, HCl treatment was performed before any purification attempt on both intermediates, to give rise to the corresponding diol compounds **3d–e** in a good yield (Table 2, entries 3 and 4). The presence of an amino group protected by a Boc group and an ester function did not deteriorate the coupling reaction. Nevertheless, it was necessary to perform a TFA deprotecting step (see ESI,† for details) to obtain the corresponding cephalosporin **3f** with a good yield and purity (Table 2, entry 5). The electronic effect was also studied with the introduction of electron-withdrawing and electron-donating groups on the arylboronic acid reagent **2**. In the case of an ester function, a rapid conversion into the expected product **3g** was observed, with a good isolated yield (Table 2, entry 6). In the case of the *N,N*-dimethylaniline boronic acid **2h**, the formation of the corresponding compound **3h** was observed, but it underwent an immediate degradation, preventing any purification (Table 2, entry 7). This chemical instability may result from hyperconjugation between the nitrogen lone pair of the aniline and the double bond of the cephalosporin, weakening the condensed ring nuclei.

Finally, the introduction of double bonds was investigated with the vinyl boronic acid **2i**. The coupling reaction led to the valuable cephalosporin-vinyl synthon **3i** (Table 2, entry 8), this compound being an industrial intermediate for the synthesis of

Table 2 Exploration of the substrate scope^a

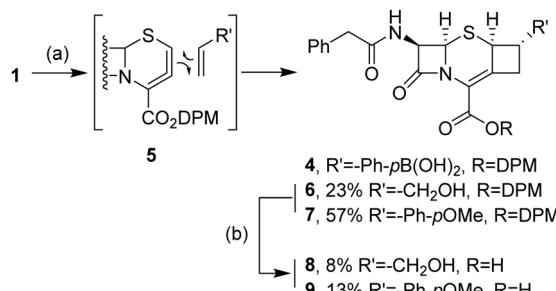
Entry	Cpd	R	Time (h)		Yield ^b (%)
			2b–i	3b–i	
1	b		1		73
2	c		1		— ^c
3	d		1		59 ^d
4	e		1		86 ^d
5	f		1		45 ^e
6	g		1		77
7	h		1		— ^f
8	i		2		74
9					65 ^g

^a Reaction conditions: **1**, 0.16 mmol, 1 eq.; **2b–g**, 1.2 eq.; Pd(OAc)₂, 10%; PPh₃, 20%; K₂CO₃, 3 eq.; THF, 3.2 mL; reflux. ^b Isolated yield. ^c No product detected by LC-MS. ^d Isolated yield after acetal deprotection (see ESI). ^e Isolated after TFA deprotection of BOC and DPM groups, see details in the ESI. ^f 100% conversion by LC-MS, but chemically unstable. ^g Gram-scale synthesis (1 g–1.58 mmol).

the marketed cefdinir (Fig. 1). To demonstrate the industrial suitability of our methodology, a gram-scale synthesis was performed and the key intermediate **3i** was obtained with a good yield (Table 2, entry 9). Obviously, a specific development will be necessary to optimize this step. Nevertheless, our approach provides a straightforward synthetic alternative, by-passing numerous costly steps, in the preparation of the 7-AVCA intermediate.²⁵

During the optimization process with the vinyl boronic acid **2a**, two recurrent side products were identified, sharing the same molecular weight and close HPLC retention times, but never detected with other boronic acid substrates **2b–i**. The Heck reaction on the vinyl group was first considered, but it was not consistent with NMR spectrum data. Finally, the structures were elucidated and consisted of cyclobutane derivative **4** as a mixture of isomers. This side-reaction has already





Scheme 1 Reaction conditions: (a) K_2CO_3 , dioxane, reflux, 1 h; (b) TFA, CH_2Cl_2 , 0 °C to rt, 1 h.

been reported in the literature and involves a [2+2] cycloaddition between the allene intermediate 5, generated by the elimination of the triflate, and the vinyl bond.^{26,27} The presence of the boronic acid function on cephalosporin 4 prevented any successful purification.

Two other analogues, with allyl alcohol and 4-vinylanisole, were investigated and led to the corresponding cyclobutene compounds 6 and 7 (Scheme 1) as pure isomers. The stereogenic center configurations were determined based on the specific NMR chemical shift, splitting signals and coupling constants, as previously established (see ESI,† for detailed NMR spectra).^{26,27} Even if this side-reaction was already known, the microbiological evaluation of the resulting fused cephalosporins has never been reported. Therefore, the DPM group was removed by acidic treatment to release the carboxylic acid, which is critical for affinity toward PBPs. Both deprotected cephalosporins 8 and 9 were submitted to MIC determination by the broth micro-dilution method toward Gram-positive and Gram-negative strains, *S. aureus* and *E. coli*, respectively (see ESI† for detailed protocols). None of them exhibited any significant antibacterial activity, probably due to the steric hindrance induced by the condensed cyclobutane ring.

3. Conclusion

To fight bacterial resistance and to always keep one step ahead of pathogens, the development of new antibiotics is crucial. In this context, the β -lactam agents, especially cephalosporin drugs, have received considerable attention in recent years, and represent the first line of defence in the current therapeutic arsenal against resistant bacteria. We developed a straightforward protocol to selectively decorate the key C3 position of the cephalosporin core, based on a Suzuki–Miyaura coupling reaction. This methodology allows synthetic access to critical described intermediates and to original motifs. The reaction can be performed at room temperature or under reflux conditions, without any detectable degradation. The scope of the reaction shows great functional-group tolerance and opens the way to a wide variety of original cephalosporin scaffolds.

Author contributions

Fanny Faure: methodology; investigation and writing – original draft; Margot Zambon: methodology and investigation; Yen Vo-

Hoang: investigation; Patricia Licznar-Fajardo: investigation; Jean-Denis Docquier: conceptualization; Suzanne Peyrottes: conceptualization and supervision; Laurent Gavara: conceptualization, writing – original draft and project administration; all authors contributed to writing – reviewing and editing.

Data availability

No data was used for the research described in the article.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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