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Synthesis of functionalised fluorinated pyridine derivatives by site-selective Suzuki-Miyaura cross-coupling reactions of halogenated pyridines

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Abstract: The Suzuki-Miyaura reaction of 2,6-dichloro-3-(trifluoromethyl)pyridine with 1 equiv of arylboronic acids resulted in site-selective formation of 2-aryl-6-chloro-3-(trifluoromethyl)pyridine. Due to electronic reasons, the reaction takes place at the sterically more hindered position. The selectivity was rationalised by DFT calculations. The one-pot reaction with two different arylboronic acids afforded 2,6-diaryl-3-(trifluoromethyl)pyridine containing two different aryl substituents. The reactions proceeded smoothly in the absence of phosphine ligands. In addition, Suzuki-Miyaura reactions of 2,6-dichloro-4-(trifluoromethyl)pyridine with one or two equivalents of arylboronic acids were carried out.

Keywords: catalysis; ligand free; organofluorine compounds; regioselectivity; Suzuki-Miyaura reaction.

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1 Introduction

Functionalised pyridine derivatives are of great importance as drugs and as agricultural products, such as herbicides, insecticides, fungicides, and plant growth regulators [1–6]. The pyridine nucleus is also present in many natural products [7–9]. Many pyridine derivatives are inhibitors of certain enzymes. For example, pyridine derivatives fused to a naphthalene ring are inhibitors of phosphodiesterase and thus used as antiasthmatic agents [10]. Certain pyridine N-oxide rings are CCR5 antagonists and used as anti-HIV-1 agents [11]. Other pyridine derivatives are PI3 kinase and p110α inhibitors [12]. Pyridines have also been reported to act as anti-tumour [13] and antifungal [14] derivatives.

The Hantzsch and the Chichibabin processes are classical pyridine syntheses and functionalisations [15, 16]. The synthesis of trifluoromethyl-substituted pyridines is a challenging task. Such molecules have been prepared by cycloaddition of nitriles with dienes [17], by cyclisation reactions of ethyl 3-amino-3-ethoxypropenoate [18], and by cyclisations of CF_3 substituted electrophiles with cyanoacetic amide [19]. 2,6-Diaryl-3-cyano-4-(trifluoromethyl)pyridines have been prepared by cyclocondensation of 1-aryl-4-trifluoro-1,3-butadienones with β-amino-β-arylacrylonitrile [20]. Recently, we have reported the synthesis of 4-trifluoromethylpyridines by cyclisation of 3-hydroxy-pent-4-yn-1-ones with urea [21]. In recent years, pyridines have been prepared by transition metal catalysed reactions [22–24]. To date, Suzuki-Miyaura reactions of polyhalogenated heterocycles have been studied [25–38]. This includes site-selective palladium catalysed cross-coupling reactions of dihalogenated