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Isonitriles as efficient ligands in Suzuki–Miyaura reaction

Didier Villemin,* Arnaud Jullien and Nathalie Bar

Laboratoire de Chimie Moléculaire et Thio-organique, ENSICAEN, Université de Basse Normandie, CNRS,
6 Boulevard du Maréchal Juin, 14050 Caen, France

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Abstract—Isonitrile palladium complexes [$(RNC)_2PdCl_2$] were prepared and tested in Suzuki reaction of 4-chloroanisol. $(AdNC)_2PdCl_2$ was found the most effective catalyst and was used in phenylation of several chloro and bromoaromatic substrates.

Many years ago, phosphorus ligands were the most effective ligands in catalysed coupling reactions. Recently, carbenic ligands have attracted a great deal of interest as transition metal ligands;[1] it is the case of *N*-heterocyclic carbenes derived from imidazole, pyrazole and triazole. In particular, Nolan and co-workers[2] has described the 2,4,6-trimethylphenylimidazol-2-ylidene, Arduengo's carbene (**1**)[3] as an effective ligand in Suzuki–Miyaura reactions[4] of a variety of aryl chlorides with boronic acids.

Isonitriles (**2**) are isoelectronic with these Arduengo's carbenes (**3**) and to our knowledge, isonitriles have not been described as ligands in Suzuki–Miyaura reaction. It is true that isonitriles are known for their insertion in reactions catalysed by the palladium.[5] The isonitrile complexes are known for a long time[6] but, they were little used as catalysts, except in the activation of silicon–silicon bonds catalysed by palladium complexes with tertiary alkyl isonitriles as spectator ligands[7] (Fig. 1).

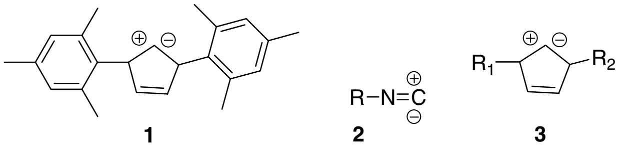
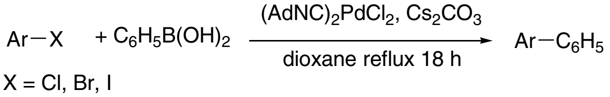


Figure 1. Analogy between carbenes (**1** and **3**) and isonitriles (**2**).

We present herein new catalysts using isonitriles as ligands in Suzuki–Miyaura reaction. We have prepared palladium complexes [$PdCl_2(RNC)_2$] of five hindered isonitriles: from *tert*-butylisonitrile (*t*-BuNC), from 1,1,3,3-tetramethylbutylisonitrile (TMBuNC), from cyclohexylisonitrile (CyNC), from 2,6-diisopropylphenylisonitrile ((iPr)$_2$PhNC) and from adamantylisonitrile (AdNC). AdNC and [(iPr)$_2$PhNC] were obtained by the Hofmann reaction[8] under phase transfer reaction from their corresponding amines.[9] The other isonitriles used (CyNC, *t*-BuNC, TMBuNC) are commercially available (Aldrich). The palladium complexes [$(RNC)_2PdCl_2$] were obtained[6] by the reaction of isonitrile (40 mmol) with palladium chloride (10 mmol) in the presence of a solution of DMF (1 mL) in acetone (20 mL), at room temperature for 24 h. These complexes [$(RNC)_2PdCl_2$] were yellow to orange, and were characterised by IR and elemental analysis. The complexes [$(RNC)_2PdCl_2$] with tertiary isonitrile are stable at room temperature. In the case of [$(CyNC)_2PdCl_2$] complex, the pale yellow complex turn to black after two weeks at room temperature.

In order to test the activity of [$(RNC)_2PdCl_2$] complexes in Suzuki–Miyaura reaction, we have chosen the reaction of 4-halogenoanisoles (Ar = p-$CH_3OC_6H_4$, X = Cl, Br, I) with phenylboronic acid[11] (Scheme 1).


$$Ar{-}X + C_6H_5B(OH)_2 \xrightarrow[\text{dioxane reflux 18 h}]{(AdNC)_2PdCl_2,\ Cs_2CO_3} Ar{-}C_6H_5$$
X = Cl, Br, I

Scheme 1. Phenylation of Ar–X by phenylboronic acid in the presence of $(RNC)_2PdCl_2$.

Keywords: Palladium catalyst; Suzuki–Miyaura reaction; Isonitrile.

* Corresponding author. Tel.: +33 231 45 28 40; fax: +33 231 45 28 77; e-mail: villemin@ensicaen.fr

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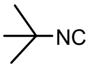
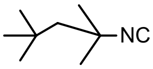
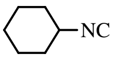
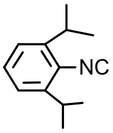
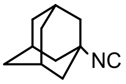
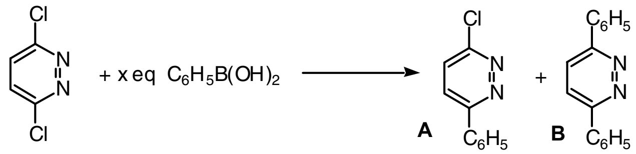
Table 1. Phenylation of X–$C_6H_4OCH_3$ by phenylboronic acid in the presence of $(RNC)_2PdCl_2$ as the catalyst (5 mol %)

R	RNC	X = I	X = Br	X = Cl
t-Bu		100	3	0
TMBu		80	3	0
Cy		93	24	2
(*i*Pr)$_2$Ph		94	24	2
Ad		100	81	8

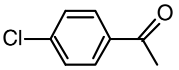
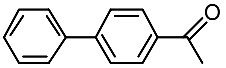
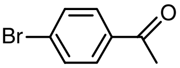
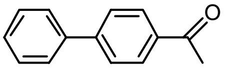
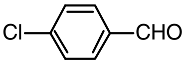
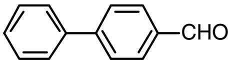
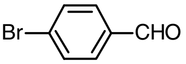
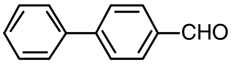
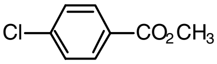
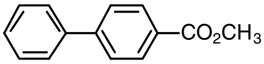
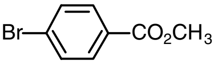
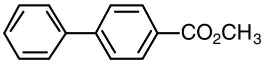
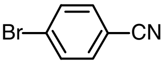
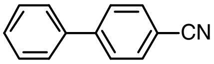
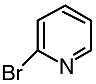
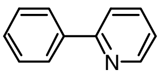
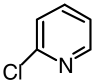
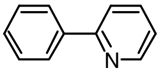
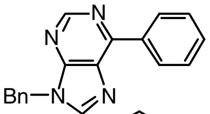
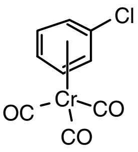
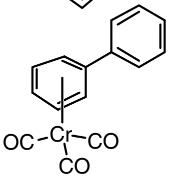
4-Halogenoanisoles are not activated electrophiles, so these reactions seem to be very appropriate for testing Suzuki–Miyaura catalyst. The results obtained[12] with different $[(RNC)_2PdCl_2]$ complexes are reported in Table 1.

$(AdNC)_2PdCl_2$ complex was the more efficient of $[(RNC)_2PdCl_2]$ complexes as catalyst in these Suzuki–Miyaura reactions. We have not observed products resulting from the insertion of isonitriles in this reaction, the isonitrile ligands behave as spectator ligands. The activity of $(AdNC)_2PdCl_2$ complex is very close to the best Arduengo's carbene palladium complex[3] or the hindered alkylphosphine palladium complexes. So we have decided to test this catalyst with halogenoaromatic or halogenoheteroaromatic substrates, especially with activated aryl or heteroarylchlorides (Schemes 1; Table 2). In the case of dichloroheterocyclic compounds, the products obtained depend on the stoichiometry of the reaction, but unfortunately, it was not possible to substitute selectively one chlorine atom (Schemes 2 and 3; Tables 3 and 4).



Scheme 2.

Table 2. Yield (%) of isolated phenylated products[12] obtained by the reaction of phenylboronic acid catalysed by $(AdNC)_2PdCl_2$

Ar–X	Ar–C_6H_5	Yield (%)
		50
		76
		67
		74
		69
		75
		65
		84
		56
		58
		94

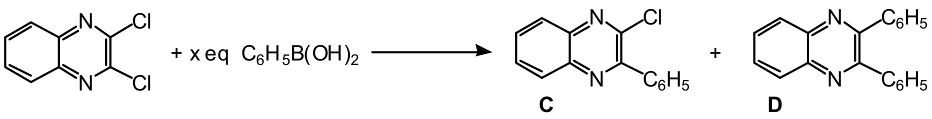
Isolated products were identified by NMR and MS.

Table 3. Arylation of 3,6-dichloropyridazine

x equiv $C_6H_5B(OH)_2$	**A** yield[13]	**B** yield (%)
1.2	50	20
2.4	Trace	69

Table 4. Arylation of 1,4-dichlorophthalazine

x equiv $C_6H_5B(OH)_2$	**C** yield[13]	**D** yield (%)
1.2	26	51
2.4	Trace	75



Scheme 3.

In conclusion, adamantylisonitrile palladium complex is an interesting catalyst in Suzuki–Miyaura reaction of bromoaromatic or heteroaromatic substrates and activated chloroaromatic and *p*-deficient heteroaromatic substrates.

Acknowledgement

We thank Miss. S. Leconte for preliminary experiments with isonitriles complexes.

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9. Isonitriles were obtained by the reaction of 1-adamantamine or diisopropylaniline with chloroform under phase transfer (NaOH 50%/toluene–chloroform/TEBACl). Diisopropylphenylisonitrile (yield 53%) as a liquid and adamantylisonitrile (yield 55%) as a white solid (mp = 186 °C after sublimation) were described.[10]
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12. Experimental: a mixture of ArX (1 mmol), $C_6H_5B(OH)_2$ (1.2 mmol), Cs_2CO_3 (2.2 mmol), $(AdNC)_2PdCl_2$ (0.05 mmol), and dioxane (5 mL) was refluxed for 18 h. Product was isolated by flash chromatography and identified by spectroscopy [GC/MS, ^1H and ^{13}C NMR].
13. All the analyses were monitored by HPLC-Q-ToF.