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Preparation of polyfunctional pyridines by a palladium(0)-catalyzed cross-coupling of functionalized aryl Grignard reagents

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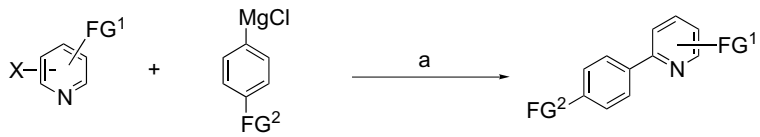
Abstract—Difunctionalized pyridines can be prepared by a Pd(0)-catalyzed cross-coupling of functionalized arylmagnesium compounds with chloro- or bromopyridines at temperatures as low as –40°C. An addition–elimination mechanism involving a palladate intermediate is proposed.

The preparation of polyfunctional heterocycles is an important synthetic goal because of the multiple applications of these molecules.[1] Transition metal cross-couplings have proven to be an important method for preparing a number of complex heterocycles.[2] The major limitation of this approach is the moderate reactivity of typical organometallics used, such couplings as organozincs, organoboronic acids or organotin derivatives.[3] More reactive organometallics suffer from a moderate functional group tolerance. Recently, we have reported a new preparation of polyfunctional aryl- and heteroarylmagnesium compounds via a halogen–magnesium exchange reaction.[4] Herein, we wish to report remarkably mild reaction conditions allowing a palladium-catalyzed cross-coupling of functionalized pyridyl halides of type **1** with functionalized arylmagnesium reagents of type **2** leading to polyfunctional pyridines of type **3** (see Scheme 1 and Table 1). Already several Stille, Suzuki and Negishi cross-coupling reactions have been reported with chloropyridines and chloroquinolines.[5] In most cases, these reactions proceed in refluxing THF. These conditions are not suitable for functionalized Grignard compounds of type **2** bearing an ester or a cyano group. More appropriate would be a related nickel-catalyzed reaction using pyridyl bromides,[6] however the toxicity of nickel salts led us to explore an alternative route.

We found that by treating phenylmagnesium chloride (**2a**: 1.2 equiv.) with ethyl 6-bromonicotinate (**1a**: 1.0 equiv.) with bis(dibenzylideneacetone)palladium(0); ($Pd(dba)_2$: 5–10 mol%) and 1,1′bis(diphenylphosphino)-ferrocene (dppf, 5–10 mol%)[7] in THF at –40°C for 6 h, a fast cross-coupling reaction is observed leading to the 6-phenyl-substituted nicotinic derivative **3a** in 95%



1 **2** **3**

Scheme 1. Cross-coupling reactions of functionalized magnesium reagents: X = Cl, Br; FG^1 = CN, CO_2Et, Br; FG^2 = H; CO_2Me, CN; (a) $Pd(dba)_2$ (5–10% mol), dppf or t-Bu_3P (5–10% mol).

Keywords: palladium-catalysis; pyridine synthesis; functionalized organomagnesium reagent; heterocycle synthesis.

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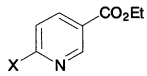
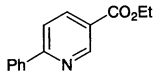
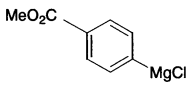
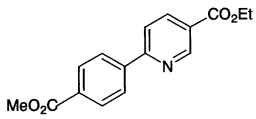
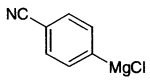
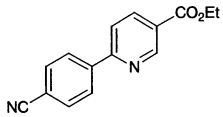
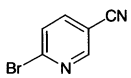
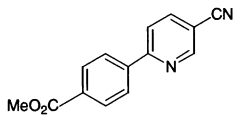
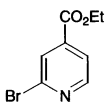
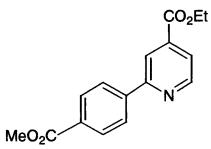
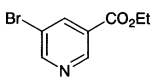
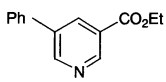
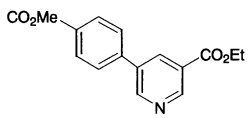
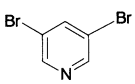
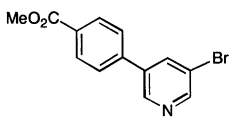
Table 1. Polyfunctional pyridines **3a**–**3h** obtained by a palladium(0)-catalyzed cross-coupling of arylmagnesium reagents with chloro- or bromo-pyridines

Entry	Grignard reagent	Pyridyl halide	Conditions (°C, h)	Product of Type **3**	Yield (%)[a]
		 **1**		 **3a**	
1	**2a**: PhMgCl	**1a**: X=Br	-40, 6		95
2	**2a**: PhMgCl	**1b**: X=Cl	-40, 6		92
3	 **2b**	**1b**	-40, 6	 **3b**	95
4	 **2c**	**1a**	-40, 6	 **3c**	87
5	**2b**	 **1c**	-40, 6	 **3d**	86
6	**2b**	 **1d**	-20, 4	 **3e**	90
7	**2a**	 **1e**	0, 18[b]	 **3f**	73
8	**2b**	**1e**	0, 18[b]	 **3g**	63
9	**2b**	 **1f**	-5,18[b]	 **3h**	62

[a] Yield of analytically pure products

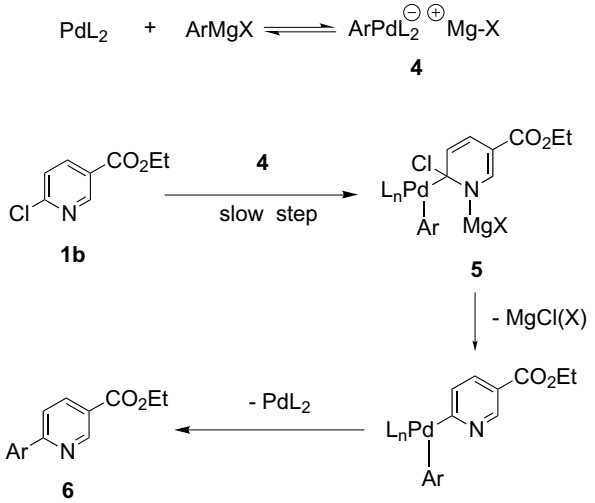
[b] This reaction has been performed with *t*-Bu_3P (10 mol%) and $Pd(dba)_2$ (10 mol%).

yield. Remarkably, the same smooth reaction is observed with the corresponding chloropyridine **1b** leading to **3a** in 92% yield (entries 1 and 2 of Table 1).

These mild conditions allow the extension of this cross-coupling to functionalized arylmagnesium compounds such as the ester-substituted Grignard reagent (**2b**) and 4-cyanophenylmagnesium chloride (**2c**). These two organometallics are stable up to 0°C. We have tested the cross-coupling reaction between 2-bromo-4-methylpyridine and phenylmagnesium chloride (**2a**) with the usual catalyst system at −25°C over 18 h. No deprotonation of the methyl group was noticed[8] and we obtained the cross-coupled product quantitatively.[9] The exceptionally fast palladium-catalyzed cross-coupling with 2-halogenopyridines can be explained assuming an addition–elimination mechanism to 2-chloropyridine (**1b**). The high electrophilicity of the pyridine facilitates

the initial addition step to PdLn or more likely of the related ate-species $ArPdLn^- MgX^+$ (**4**) obtained by the reaction of PdL_2 with the Grignard reagent leading to the stabilized magnesium amide **5**, which after elimination of a chloride and subsequent reductive elimination furnishes the product **6** (Scheme 2).[10] We have observed that the cross-coupling reaction proceeds under such mild conditions only when using an arylmagnesium reagent. The corresponding arylzinc derivative does not react under the same conditions and only gives a slow reaction at higher temperature (0°C) supporting that the oxidative addition may involve the palladate species **4**. Organozinc reagents have less tendency to form ate-species due to the more covalent nature of the C–Zn bond. The importance of the carbethoxy group in position **3**, which is able to stabilize the excess negative charge of **5** by resonance, can be established since the corresponding 4-substituted carbethoxy-2-bromopyridine reacts only at −20°C with the Grignard reagent **2b** leading to the cross-coupling product **3e** in 90% yield (entry 6 of Table 1).[11] No reaction occurs in the absence of the palladium(0) catalyst. 3-Halo-substituted pyridines also react but since the extra-stabilization due to the formation of an intermediate of type **5** is no longer possible, higher temperatures are required for the cross-coupling. In these cases it has been advantageous to use t-Bu_3P as ligand[12] (10 mol%). Under these conditions a cross-coupling with phenylmagnesium chloride (**2a**) and 4-carbomethoxyphenylmagnesium chloride (**2b**) can be achieved at 0°C within 18 h in good yields (63–73%; entries 7 and 8).

In summary, we have found very mild reaction conditions allowing the palladium-catalyzed cross-coupling of functionalized arylmagnesium compounds with various chloro- and bromo-pyridines leading to polyfunctional pyridines which are of interest for various pharmaceutical applications.



Scheme 2. Possible mechanism for the Pd(0)-catalyzed substitution of 2-chloropyridines by arylmagnesium compounds.

Acknowledgements

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11. Typical procedure, preparation of methyl 4-(5-cyano-2-pyridyl) benzoate (**3d**): Isopropylmagnesium chloride (2 M, 1.2 mmol in ether) was added to a solution of methyl 4-iodobenzoate (1.2 mmol) in THF (4 mL) at −40°C under argon and the mixture was stirred for 40 min leading to the functionalized arylmagnesium chloride. The resulting mixture was transferred into a solution of 2-bromo-5-cyanopyridine (**1c**) (1 mmol), bis(dibenzylideneacetone)palladium(0) (5.0 mol%) and 1,1′-bis(diphenylphosphino)ferrocene (5.0 mol%) in THF (2 mL) at −40°C. Stirring was continued at this temperature for 6 h followed by quenching using an aqueous saturated NH_4Cl solution (5 mL). Extraction by diethyl ether, drying over $MgSO_4$ and solvent removal afforded a crude solid, which was purified by flash chromatography on silica (elution with CH_2Cl_2) affording the pure product **3d** as a white solid (mp = 162°C, 210 mg, 86% yield).
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