Journal of Organometallic Chemistry 694 (2009) 455–465

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Palladium-catalyzed direct heteroarylation of chloropyridines and chloroquinolines

Fazia Derridj [a], Julien Roger [b], Florence Geneste [b], Safia Djebbar [a], Henri Doucet [b,*]

[a] Laboratoire d'hydrométallurgie et chimie inorganique moléculaire, Faculté de Chimie, U.S.T.H.B. Bab-Ezzouar, Alger, Algeria
[b] Institut Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes "Catalyse et Organometalliques", Campus de Beaulieu, 35042 Rennes, France

ARTICLE INFO

Article history:
Received 8 September 2008
Received in revised form 27 October 2008
Accepted 14 November 2008
Available online 24 November 2008

Keywords:
Aryl chlorides
Catalysis
C–H activation
Heteroarenes
Palladium

ABSTRACT

The direct coupling of aryl chlorides with heteroarenes would be a considerable advantage for sustainable development due to their lower cost, lower mass, the wider diversity of available compounds and also because of the formation of only HCl associated to a base as by-product and the reduction of the number of steps to prepare these compounds. We observed that through the use of $PdCl(dppb)(C_3H_5)$ as a catalyst, a range of heteroaryl derivatives undergoes coupling via C–H bond activation/functionalization reaction with chloropyridines or chloroquinolines in low to high yields. This air-stable catalyst can be used with a wide variety of substrates. The position of the chloro substituent on pyridines has a minor influence on the yields. On the other hand, the nature on the heteroaryl derivative has a large influence. The highest yields were obtained using benzoxazole, thiophene or thiazole derivatives. The coupling of chloropyridines with furans also gave the expected products, but in low to moderate yields.

1. Introduction

The palladium-catalyzed cross-coupling reactions between pyridyl halides and heteroarenes represent a powerful access to heteroarylated pyridines, which are important pharmaceutical compounds [1]. Negishi [2], Stille [3], Kumada [4] or Suzuki [5] cross-coupling reactions have been largely employed for the preparation of such compounds. However, these methods are not very convenient due to the limited access and various stabilities of several heteroaromatic organometallic derivatives. Moreover, these reactions are not environmentally attractive as they provides an organometallic or salt (MX) as by-product. Over the last years, very interesting results for the coupling of pyridyl halides with heteroaromatic derivatives by C–H bond activation have been reported and provide an economically and environmentally attractive procedure for the preparation of such compounds [6]. However, so far most of the results were obtained with reactive, but expensive bromopyridines or iodopyridines [7–10]. The use of chloropyridines for such coupling reactions would be a considerable advantage for sustainable development due to their lower cost, lower mass and the wider diversity of available compounds. This reaction provides only HCl associated to a base as by-product and therefore is very interesting both in terms of atom-economy and inert wastes. However, for this coupling, aryl chlorides are relatively uncommon partners [11]. This is due to the fact that the oxidative addition of pyridyl chlorides to palladium is slower than with bromides or iodides. One of the first examples of such reaction was reported by Zhuravlev [11a]. He observed that the coupling product of 2-chloropyridine with an oxazolopyridine derivative could be obtained in 33% yield using $Pd(OAc)_2$ (5 mol%) / PPh_3 (20 mol%), Cs_2CO_3 and acetone as reaction conditions. Better yields were obtained using palladium associated to electron-rich monophosphines. For example, Daugulis and co-worker have been able to couple 2-chloro-6-methoxypyridine with benzothiophene in 72% yield using $Pd(OAc)_2$ (5 mol%)/butyldi-1-adamantylphosphine (10 mol%) as catalyst. This catalyst also gave good results for the coupling of 2-chloropyridine with benzoxazole [11b]. A relatively similar procedure has been described recently for the 2-arylation of a 4-thiazolecarboxylate. Using 5–10 mol% $Pd(OAc)_2$ and 10–20 mol% P(biphenyl-2-yl)Cy_2 as catalyst, the coupling of 2-chloro and 3-chloropyridines gave the expected products in high yields [11d].

If monophosphine ligands such as PPh_3 or the air-sensitive P(biphenyl-2-yl)Cy_2 and butyldi-1-adamantylphosphine have been successfully used for the direct coupling of heteroaromatics with pyridyl chlorides, the efficiency of bidentate phosphine ligands for such couplings has not been demonstrated. Moreover, it should be noted that, so far, relatively few pyridyl chloride derivatives and heteroaromatics have been employed for this reaction [11]. For example, to our knowledge, the 2-arylation of furans and the 5-arylation of thiazoles using pyridyl chlorides or the reactivity of 4-chloropyridines have not been reported. Therefore, the discovery of an effective and selective method, using a low loading of an air-stable catalyst, for the direct coupling of both electron-excessive and electron-deficient 2-, 3- or 4-pyridyl chlorides with a wide variety of heteroaromatics still needs to be developed.

* Corresponding author. Tel.: +33 2 23 23 63 84; fax: +33 2 23 23 69 39.
E-mail address: henri.doucet@univ-rennes1.fr (H. Doucet).

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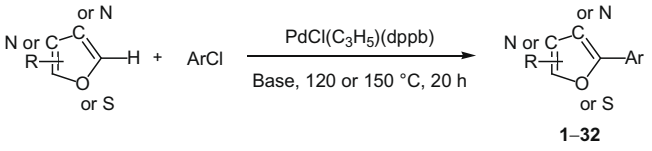
doi:10.1016/j.jorganchem.2008.11.032

So far, most of the coupling reactions of heteroaryl derivatives with aryl chlorides *via* a C–H bond activation require relatively high catalyst loadings (1–10 mol%) and have been performed at elevated temperature (120–150 °C) [6]. At these temperatures, when $Pd(OAc)_2$ is employed as catalyst precursor, soluble palladium(0) colloids or nanoparticles are generally formed, and then, especially under high palladium concentrations (typically when 1–10 mol% catalyst is employed), so-called "palladium black" forms rapidly. This "palladium black" is inactive for the coupling of most aryl chlorides with arenes. Therefore, for the direct coupling of chloropyridines with aryl chlorides, the stabilization of monomeric palladium species or small clusters is necessary. Such stabilization can be performed using either ammonium salts or ligands. Consequently, we have prepared the air-stable $PdCl(C_3H_5)$(dppb) complex (dppb = 1,4-bis(diphenylphosphino)butane) [12]. The idea was that intermediate Pd(0) species have to be protected by internal ligation against decomposition pathways through under-ligation and subsequent colloid and "Pd black" formation [13–16]. The presence of the bidentate ligand dppb on palladium might also reduce the poisoning of the catalyst due to the presence of heteroaromatics. We have already reported some results for the direct coupling of heteroaromatics with aryl and vinyl bromides [14,15] and also with aryl chlorides [9e,11c] using this catalyst. Herein, we report that this catalyst provides a powerful system for the cross-coupling of chloropyridine or chloroquinoline derivatives with a wide variety of heteroaromatics.

2. Results and discussion

We describe here successively the reactions of 2-chloro, 3-chloro and 4-chloropyridine derivatives with a range of heteroaromatics (Scheme 1, Tables 1–4). We initially examined the influence of several reaction parameters on the yield for the coupling of 2-chloropyridine with benzoxazole or 2-*n*propylthiazole (Table 1). The best results for the reaction with benzoxazole were obtained using Cs_2CO_3 associated to DMF and $PdCl(C_3H_5)$(dppb) as catalyst at 150 °C (Table 1, entry 4). With this substrate, KOAc as base or ligand-free catalysts gave very low yields of target product (Table 1, entries 1, 2, 6 or 7). In absence of catalyst no formation of product was detected by GC (Table 1, entry 9). On the other hand, with 2-*n*propylthiazole, the highest yield was obtained using KOAc as base and DMAc as solvent (Table 1, entry 13). The reactions conducted at 100 °C instead of 150 °C gave lower yields (Table 1, entries 5 and 14).



Scheme 1.

Therefore, for this study, DMF and Cs_2CO_3 were chosen as reaction conditions for the 2-arylation of benzoxazole and benzothiazole. For the 5-arylation of thiazoles, thiophenes or furans, DMAc and KOAc were employed as the solvent and the base. The reactions were performed under argon in the presence of 2.5 mol% of $PdCl(C_3H_5)$(dppb) as catalyst. Most of the substrates and products are thermally stable so, in order to obtain higher yields, we have performed the reactions at an elevated temperature: 150 °C. However, in some cases, a lower reaction temperature of 120 °C had to be employed due to partial decomposition of the starting material or coupling product.

First, we tested several reaction conditions for the coupling of 2-chloropyridines with seven heteroaromatics (Table 2). 2-Chloro-6-methylpyridine, 2-chloropyridine or 2-chloroquinoline reacted with benzoxazole gave the target products 1–3 in 65–79% yields (Table 2, entries 1–3). To determine the electronic influence of the pyridine substituents on this coupling reaction, we studied the reactivity of substituted 2-chloropyridines. The presence of electron donating or withdrawing substituents appears to have a minor effect on the reaction yields. 5-Trifluoromethyl-2-chloropyridine and 6-methoxy-2-chloropyridine gave the expected coupling products 4 and 5 in similar yields of 77% and 78%, respectively (Table 2, entries 4 and 5). Then, we studied the 2-arylation of benzothiazole using 2-chloropyridines. We obtained lower yields of desired products than in the presence of benzoxazole. However, the target compounds 6-8 were formed in all cases using either 2-chloro-6-methylpyridine, 2-chloroquinoline or 5-trifluoromethyl-2-chloropyridine (Table 2, entries 6–8). In the literature, the 2-arylation of a 4-thiazolecarboxylate using pyridyl chlorides has been reported [11d]. In order to extend the scope of this reaction; we examined the 5-arylation of 2-substituted thiazoles. 2-*n*Propylthiazole was coupled with 2-chloropyridine, 2-chloroquinoline or 6-methoxy-2-chloropyridine. As expected, the 5-arylated thiazoles 9–11 were selectively obtained in 38–64% yields (Table 2, entries 9–11). In the same manner, two 2,4-substituted thiazoles: 2-ethyl-4-methylthiazole and 2-phenyl-4-methylthiazole were reacted affording 12–14 in very similar yields (Table 2, entries 12–14). Finally, the reactivity of 2-substituted thiophenes with 2-chloro-6-methoxypyridine has been studied, and again,

Table 1
Palladium-catalyzed direct arylation of 2-chloropyridine, influence of the reaction conditions.

Entry	Heteroarene	Base	Solvent	Catalyst	Temperature (°C)	Yield (%)[a]
1	Benzoxazole	KOAc	DMF	$PdCl(C_3H_5)$(dppb)	150	27
2	Benzoxazole	KOAc	DMAc	$PdCl(C_3H_5)$(dppb)	150	5
3	Benzoxazole	Cs_2CO_3	DMAc	$PdCl(C_3H_5)$(dppb)	150	67
4	Benzoxazole	Cs_2CO_3	DMF	$PdCl(C_3H_5)$(dppb)	150	72 (69)
5	Benzoxazole	Cs_2CO_3	DMF	$PdCl(C_3H_5)$(dppb)	100	25
6	Benzoxazole	Cs_2CO_3	DMF	$Pd(OAc)_2$	150	3
7	Benzoxazole	Cs_2CO_3	DMF	$[PdCl(C_3H_5)]_2$	150	2
8	Benzoxazole	Cs_2CO_3	DMF	$[PdCl(C_3H_5)]_2$/2 PPh_3	150	58
9	Benzoxazole	Cs_2CO_3	DMF	–	150	0
10	2-*n*propylthiazole	KOAc	DMF	$PdCl(C_3H_5)$(dppb)	150	26
11	2-*n*propylthiazole	Cs_2CO_3	DMAc	$PdCl(C_3H_5)$(dppb)	150	2
12	2-*n*propylthiazole	Cs_2CO_3	DMF	$PdCl(C_3H_5)$(dppb)	150	12
13	2-*n*propylthiazole	KOAc	DMAc	$PdCl(C_3H_5)$(dppb)	150	45 (38)
14	2-*n*propylthiazole	KOAc	DMAc	$PdCl(C_3H_5)$(dppb)	100	2

[a] Conditions: catalyst: [Pd] (0.025 mmol), 2-chloropyridine (1 mmol), heteroarene (1.2 mmol), base (1.2 mmol), solvent (5 mL), 20 h, GC and NMR yields, yields in parenthesis are isolated.