Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 5283–5286

Use of highly reactive, versatile and air-stable palladium–phosphinous acid complex $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ (POPd) as a catalyst for the optimized Suzuki–Miyaura cross-coupling of less reactive heteroaryl chlorides and arylboronic acids

Subhash P. Khanapure* and David S. Garvey

NitroMed, Inc., Department of Chemistry, 12 Oak Park Drive, Bedford, MA 01730, USA

Received 12 March 2004; revised 3 May 2004; accepted 4 May 2004

Abstract—Using highly reactive air-stable palladium–phosphinous acid complex $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ (POPd) as a catalyst, synthesis of heteroaryl–aryl cross-coupled products via palladium-catalyzed Suzuki–Miyaura coupling of less reactive substituted 3-chloropyridines with arylboronic acids was achieved in high yields.

In the past decade, the synthesis of biaryl compounds by palladium-catalyzed cross-coupling reaction between aryl triflates or aryl halides with arylboronic acids, commonly referred to as the Suzuki–Miyaura coupling has developed into an extremely powerful synthetic method in organic synthesis.[1,2] It is noteworthy to mention that besides the published work in scientific journals,[3,4] the patent literature on the utilization of Suzuki–Miyaura cross-coupling reaction is extensive. For example, pharmaceutical companies utilized this cross-coupling as a cornerstone reaction in generating extensive libraries of *ortho*-diarylsubstituted five- or six-membered ring compounds for the development of potent cyclooxygenase-2 (COX-2) selective inhibitors. The biaryl group is also a key pharmacophore in the sartan class of anti-hypertensive drugs.[5,6] Of the various cross-coupling reactions, Suzuki–Miyaura cross-coupling has a practical advantage over other cross-coupling methods due to the commercial availability of a wide variety of arylboronic acids, which are nontoxic, as well as air- and moisture-stable.

One of the early limitations of the Suzuki–Miyaura cross-coupling reaction was the poor reactivity of heteroaryl chlorides. To overcome this limitation, a versatile catalyst $Pd_2(dba)_3/P(t\text{-Bu})_3$ that catalyzes the coupling reaction of less reactive aryl chlorides and arylboronic acids under mild conditions,[7] and the use of sterically hindered ligands such as 2-(dicyclohexylphosphino)biphenyl[8] were later discovered. Li and co-workers developed the air-stable palladium–phosphinous acid complexes, for example, $[(t\text{-Bu})_2P(OH)]_2PdCl_2$, $[(t\text{-Bu})P(OH)PdCl_2]_2$, and $\{[(t\text{-Bu})_2PO\text{–}H\text{–}OP(t\text{-Bu})_2]PdCl\}_2$ abbreviated as POPd, $POPd_1$, and $POPd_2$, that were investigated and found to be efficient catalysts for a variety of cross-coupling reactions of less reactive aryl chlorides and arylboronic acids.[9–11]

During the course of our efforts to synthesize novel cyclooxygenase-2 selective inhibitors[12] the need to find efficient conditions for the Suzuki–Miyaura cross-coupling reaction of substituted 3-halopyridines with arylboronic acids was required.[13] Although bromide displacements are facile in pyridine systems independent of the position of the halide using a traditional palladium catalyst[14] such as $Pd(PPh_3)_4$, the bromopyridines are available commercially only in small quantities and are expensive.

Accordingly, we devised a method optimizing the reaction conditions for the less reactive chloropyridyl compounds. We found that substituted-2-chloropyridines reacted with arylboronic acids using the classical

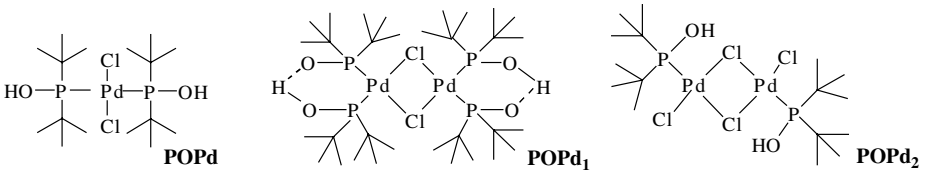
Keywords: Suzuki–Miyamura; 3-Chloropyridines; Arylboronic acids; POPd; Cyclooxygenase.
* Corresponding author. Tel.: +1-781-6859711; fax: +1-781-2751127; e-mail: skhanapure@nitromed.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.010

$Pd(PPh_3)_4$ catalyst and sodium carbonate as a base to give the desired products in high yields, as shown in Eq. 1 (Figure 1).[13] However, under the identical conditions, reactions of 3-chloropyridines with arylboronic acids failed to yield any of the desired products (Eq. 2). While one might anticipate that 2-position of pyridine would be more electron deficient than the 3-position, and therefore substituted 2-chloropyridines would be better substrates using the $Pd(PPh_3)_4$ catalyst, the total lack of reactivity for substituted 3-chloropyridines was unexpected. Very recently, a similar observation has been reported (2% yield) during the reaction of 3-chloropyridine and phenylboronic acid using a heterogeneous catalyst, palladium/charcoal.[14] However, the yield of the reaction was dramatically improved[14] using the palladium/charcoal catalyst and a sterically hindered ligand 2-(dicyclohexylphosphino)biphenyl.[8]

When we used the $Pd_2(dba)_3/(t\text{-}Bu)_3P$ catalyst,[7] reactions did not go to completion, and the desired cross-coupling products were obtained in low, variable yields (15–20%) (Eq. 3).[13] It has been reported that the 1:1 ratio of $Pd_2(dba)_3$ catalyst and $(t\text{-}Bu)_3P$, which generates in situ the reactive palladium–monophosphine complex is also critical to give the optimum yields since the use of catalyst and phosphine reagent in a 1:2 ratio leads to an extremely slow reaction. From synthetic and process-development viewpoint, it appeared to us that it would be advantageous to explore further the scope and limitations of the POPd catalysts.[11] Direct use of POPd as a catalyst would also be practical considering the difficulties and variability associated with the generation of active catalysts in situ and the handling of extremely air-sensitive phosphine ligands. Recently, POPd, $POPd_1$, and $POPd_2$ catalysts have been utilized in Stille reactions of 4-chloroquinolines and aryl stannanes, in Heck additions of aryl chlorides to *t*-butyl acrylates,[15] and in regioselective Suzuki coupling of 2,6-dichloronicotin amides.[16]

The principal goal of this study was to explore the possibility of using the air-stable POPd catalysts,[17] in the Suzuki–Miyaura cross-coupling reaction of substituted 3-chloropyridines with arylboronic acids to afford heteroaryl–aryl frameworks that were either not possible or difficult to generate using other Pd-catalysts. In this paper, we report the cross-coupling reactions of substituted-3-chloropyridines with a variety of arylboronic acids where the POPd catalysts played a significant role in giving the desired cross-coupled products in high yields, as shown in Eq. 4.



The substituted 3-chloropyridine **1** coupled with a variety of arylboronic acids such as **2a**–**d** to give corresponding cross-coupled products **3a**–**d** in good yields (75–98%) (Table 1). The scope and limitations of this reaction were further investigated by performing the reactions of various 3-chloropyridines **4**, **7**, and **10** with a variety of arylboronic acids **5**, **8**, and **2a**. The results are summarized in Table 1. The yields mentioned in the Table 1 are for either recrystallized or chromatographically purified products and we have not made attempts to investigate use of other bases or the solvents in the reaction to further optimize the yields.

It is important to note that **3d** could be obtained in 98% yield using POPd as the catalyst in the reaction.[18]

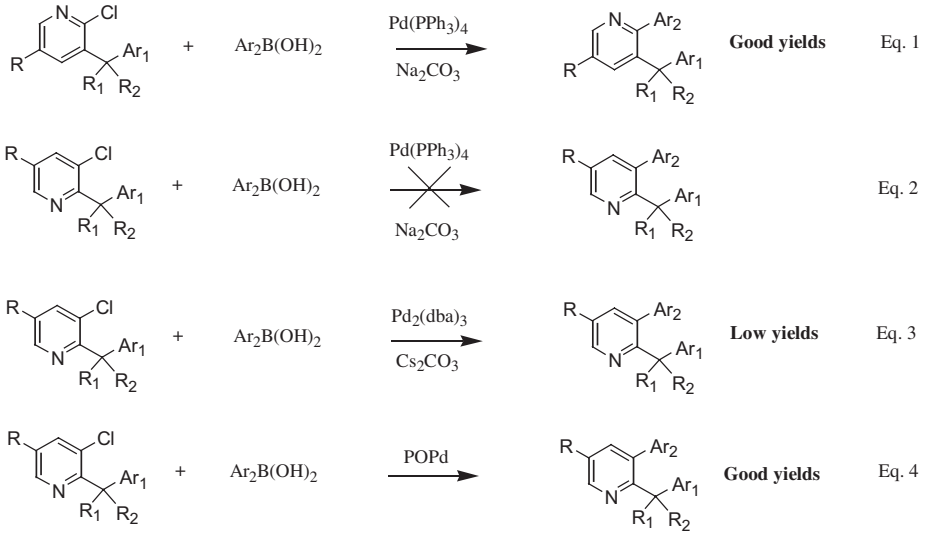
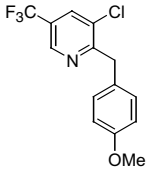
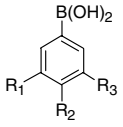
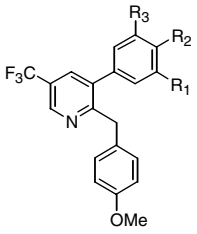
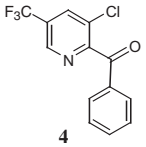
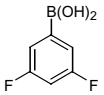
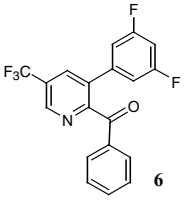
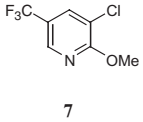
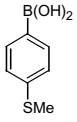
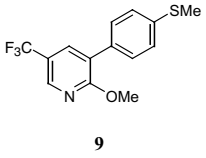
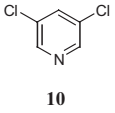
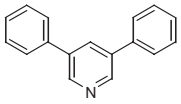


Figure 1.

Table 1. Examples of Suzuki–Miyaura cross-coupling products using POPd as a catalyst[a]

Substrate	Arylboronic acid	Product	Yield[b] (%)
 **1**	 **2a**; $R_1 = R_2 = R_3 = H$ **2b**; $R_1 = R_3 = H$; $R_2 = F$ **2c**; $R_1 = R_2 = H$; $R_3 = F$ **2d**; $R_1 = R_3 = H$; $R_2 = SO_2Me$		**3a**; $R_1 = R_2 = R_3 = H$ 91 **3b**; $R_1 = R_3 = H$; $R_2 = F$ 75 **3c**; $R_1 = R_2 = H$; $R_3 = F$ 94 **3d**; $R_1 = R_3 = H$; $R_2 = SO_2Me$ 98
 **4**	 **5**	 **6**	79
 **7**	 **8**	 **9**	98
 **10**	**2a**	 **11**	74[c]

[a] All reactions were conducted using 1.5 equivalents of arylboronic acid, 3 equivalents of Cs_2CO_3, and 0.025 mol% POPd. Most reactions were >1/2 complete in 1 h and complete in 4 to 8 h, but can be allowed to run overnight for convenience.
[b] Isolated yields of pure products.
[c] 3 Equivalents of arylboronic acid, 4 equivalents of Cs_2CO_3, and 0.05 mole% POPd were used.

In comparison, the traditional $Pd(PPh_3)_4$ catalyst under the standard Suzuki reaction conditions completely failed to give any of the coupled product (Eq. 2). When the $Pd_2(dba)_3/(t\text{-}Bu)_3P$ catalyst was employed, the reaction did not go to completion and the desired product was obtained in low yield (Eq. 3). It is interesting to note that in the presence of POPd catalyst, the reaction of 3,5-dichloropyridine **10** with phenylboronic acid **2a** afforded **11** in 74% yield. This demonstrates that the arylboronic acid can effectively cross-couple with both deactivated positions of the pyridine ring when this catalyst is employed in the cross-coupling reaction. In regard to comparisons of catalytic effects of POPd, $POPd_1$, and $POPd_2$, we performed the reaction of compounds **7** and **8** (Table 1), using these catalysts. The cross-couplings were equally effective under identical conditions of concentration and temperature. Based upon these results, the POPd catalysts have been found to be superior reagents in the cross-coupling reactions of 3-chloropyridines with arylboronic acids. Additionally, due to the air-stability of the POPd catalysts, they are much more convenient to handle and thus offer an attractive alternative for the chemists interested in exploring their use in the Pd-catalyzed reactions in organic synthesis.

In conclusion, we have demonstrated that Suzuki–Miyaura coupling of less reactive 3-chloropyridines with a variety of arylboronic acids proceeds in high yield using the palladium–phosphinous acid complex POPd as a catalyst. The further usefulness of this catalyst for the synthesis of COX-2 selective inhibitors is currently under investigation in our laboratories.

Acknowledgements

We thank Dr. Li, at CombiPhos Catalysts, Inc., Princeton, NJ, for helpful discussions regarding the use of POPd catalyst.

References and notes

1. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519.
2. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
3. Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.
4. Miyaura, N. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1998; Vol. 6, pp 187–243.
5. Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151–8156.
6. Goa, K. L.; Wagstaff, A. J. *Drugs* **1999**, *51*, 820–845.
7. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
8. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
9. Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677–8681.
10. Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513.
11. Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643–3650.
12. Khanapure, S. P.; Garvey, D. S.; Young, D. V.; Ezawa, M.; Earl, R. A.; Gaston, R. D.; Fang, X.; Murty, M.; Martino, A.; Shumway, M.; Trocha, M.; Marek, P.; Tam, S. W.; Janero, D. R.; Letts, L. G. *J. Med. Chem.* **2003**, *46*, 5484–5504.
13. Khanapure, S. P.; Augustyniak, M.; Garvey, D. S.; Gordon, L. G.; Martino, A.; Murty, M.; Schwalb, D. J.; Shumway, M.; Trocha, M.; Young, D. V.; Zemtseva, I. S.; Janero, D. R. *J. Med. Chem.* (submitted for publication).
14. Tagata, T.; Nishida, M. *J. Org. Chem.* **2003**, *68*, 9412–9415.
15. Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7077–7084.
16. Yang, W.; Wang, Y.; Corte, J. R. *Org. Lett.* **2003**, *5*, 3131–3134.
17. POPd catalysts are commercially available from Combi-Phos Catalysts, Inc., Princeton, NJ 08542.
18. *Representative experimental procedure*: To a solution of **1** (2 mmol) in DME (8 mL) was added **2d** (500 mg, 2.5 mmol) followed by Cs_2CO_3 (5 mmol) and POPd (25 mg, 0.05 mmol, 0.025 mol%). The reaction mixture was refluxed for 4 h, then filtered, and the filtrate was evaporated at reduced pressure. The residue was extracted with ethyl acetate, washed with aqueous saturated Na_2CO_3, water, brine, and then dried. The solvent was evaporated, and the residue obtained was triturated with hexane–ether (9:1) to give pure product **3d** (98%) as a colorless solid, mp 104–107 °C. ^{1}H NMR ($CDCl_3$) δ 8.97 (s, 1H), 8.06 (d, $J = 8.3$ Hz, 2H), 7.79 (s, 1H), 7.47 (d, $J = 8.3$ Hz, 2H), 6.91 (d, $J = 8.6$ Hz, 2H), 6.8 (d, $J = 8.6$ Hz, 2H), 4.15 (s, 2H), 3.81 (s, 3H), 3.17 (s, 3H); LRMS (APIMS) m/z 422 $(M+H)^+$.