DOI: 10.1002/ejic.200700420

Activated Aryl Chlorides: Useful Partners for the Coupling with 2-Substituted Thiazoles in the Palladium-Catalysed C-H Activation/Functionalisation Reaction

Aditya L. Gottumukkala[a] and Henri Doucet*[a]

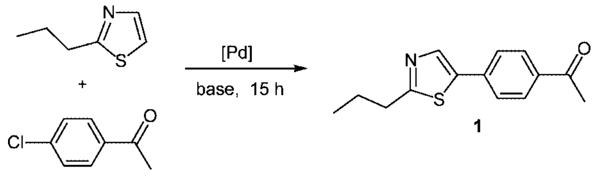
Keywords: Aryl chlorides / Catalysis / C-H activation / Palladium / Thiazoles

Aryl chlorides are noticeably uncommon partners in coupling reactions with heteroaromatics through C-H activation. We report herein that as little as 1 mol-% of the air-stable $PdCl(dppb)(C_3H_5)$ complex catalyses the direct coupling of electron-deficient aryl chlorides with 2-substituted thiazole derivatives. A range of functionalities on the aryl chloride such as acetyl, formyl, ester, nitro, nitrile or trifluoromethyl is tolerated.

Introduction

Arylthiazole derivatives are important building blocks in organic synthesis.[1] Palladium catalysed Suzuki, Stille or Negishi cross-coupling reactions are probably the most important methods for the synthesis of such compounds.[1–4] However, these reactions require the preparation of an organometallic derivative and they provide an organometallic salt (MX) as a byproduct.

Over the last few years, very interesting results for the coupling of aryl bromides or iodides with thiazole derivatives by C-H activation have been reported and provide an economically and environmentally attractive procedure for the preparation of such compounds.[5] So far, most of the results described for this reaction were obtained with reactive, but expensive aryl bromides[6] or iodides.[7] The use of chloride substrates for cross-coupling reactions with thiazoles by C–H bond activation (Scheme 1) would be a considerable advantage for sustainable development because of their lower cost, lower mass and the wider diversity of available compounds.[8–11] However, for this coupling, aryl chlorides are noticeably uncommon partners. This is due to the fact that chlorides were generally found to be unreactive under the experimental conditions employed to activate iodide and bromide analogues. In most cases, for Suzuki, Heck or Sonogashira reactions aryl chlorides were activated using electron-rich, sterically hindered, monodentate phosphane ligands associated to palladium.[11a] Moreover, in most cases, the direct coupling of aryl chlorides with heteroaromatics such as pyridines, thiophenes or thiazoles were performed with the use of relatively large amounts of palladium or ruthenium catalysts (2.5–10 mol-%).[7–10,12] Therefore, the discovery of more effective conditions, with the use of a lower catalyst loading for the coupling of thiazoles with these challenging substrates is still subject to significant improvement.



1

Scheme 1.

Monophosphane ligands associated to palladium were successfully used for the direct coupling of thiazoles derivatives with aryl bromides or iodides,[5] but the efficiency of bidentate phosphane ligands for such a coupling reaction has attracted less attention.[7c] In the literature, most of the couplings of heteroaryl derivatives with aryl halides were performed at elevated temperatures (140–150 °C).[5] At these temperatures, fast decomposition of the palladium complexes associated to monophosphane ligands generally occurs. In some cases, the use of polydentate ligands seems to increase the stability and longevity of the catalyst, so we could expect better conversions of aryl chlorides by using bidentate ligands.[13]

Results and Discussion

First, we examined the efficiency of $[PdCl(C_3H_5)]_2$ associated to mono- or bidentate ligands on the yield of the direct coupling of 4-chloroacetophenone with 2-*n*-propylthiazole (Scheme 1, Table 1). $[PdCl(C_3H_5)]_2$ associated to

---

[a] Institut Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes, "Catalyse et Organometalliques",
Campus de Beaulieu, 35042 Rennes, France
Fax: +33-2-23236939
E-mail: henri.doucet@univ-rennes1.fr

Supporting information for this article is available on the WWW under http://www.eurjic.org or from the author.

Table 1. Palladium-catalysed cross-coupling of 2-*n*-propylthiazole with 4-chloroacetophenone (Scheme 1). Conditions: catalyst 1 mol-%, 4-chloroacetophenone (1 equiv.), 2-*n*-propylthiazole (2 equiv.), base (4 equiv.), 15 h, GC and NMR yields.

Entry	Catalyst	Solvent	Base	Temperature [°C]	Yield [%][a]
1	0.5 $[PdCl(C_3H_5)]_2$/dppe	dmac	AcOK	150	41
2	0.5 $[PdCl(C_3H_5)]_2$/dppf	dmac	AcOK	150	10
3	$PdCl(dppb)(C_3H_5)$	dmac	AcONa	150	72
4	$[PdCl(C_3H_5)]_2/2PPh_3$	dmac	AcOK	150	58[b]
5	$Pd(OH)_2/C$	dmac	AcONa	150	9
6	10% Pd/C	dmac	AcOK	150	0
7	$Pd(OAc)_2$/dppb	dmac	AcOK	150	10
8	$Pd(OAc)_2/2PPh_3$	dmac	AcOK	150	6
9	$PdCl(dppb)(C_3H_5)$	dmac	AcOK	150	65 (53)
10	$PdCl(dppb)(C_3H_5)$	dmac	Cs_2CO_3	150	12
11	$PdCl(dppb)(C_3H_5)$	dmac	K_2CO_3	150	15
12	$PdCl(dppb)(C_3H_5)$	dmac	KF	150	12
13	$PdCl(dppb)(C_3H_5)$	dmf	AcONa	150	34
14	$PdCl(dppb)(C_3H_5)$	dmso	AcONa	150	17
15	$PdCl(dppb)(C_3H_5)$	nmp	AcOK	150	17
16	$PdCl(dppb)(C_3H_5)$	dioxane	AcOK	150	14[c]
17	$PdCl(dppb)(C_3H_5)$	xylene	AcOK	150	5[c]
18	$PdCl(dppb)(C_3H_5)$	dmac	AcOK	130	32
19	$PdCl(dppb)(C_3H_5)$	dmac	AcOK	170	6

[a] Yield in parenthesis is isolated yield. [b] The formation of side products was also observed. [c] Reaction performed in an autoclave.

the dppe or 1,1′-dppf ligands led to low conversions of 41 and 10%, respectively (Table 1, Entries 1 and 2). On the other hand, we observed that with $PdCl(C_3H_5)(dppb)$[14] as the catalyst, dmac as the solvent, AcONa as the base and heated 150 °C, 5-(4-acetylphenyl)-2-propyl-thiazole (**1**) was obtained with 72% conversion (Table 1, Entry 3). The dppb ligand is known to give sterically more hindered complexes than those of 1,1′-dppf or dppe. By using PPh_3 as the ligand, the formation of **1** was observed in 58% conversion together with the formation of a side product (Table 1, Entry 4). The palladium source also has a large influence on the yield. The use of $Pd(OAc)_2$ led to reactions with lower yields than those with $[PdCl(C_3H_5)]_2$ (Table 1, Entries 7 and 8). Pd/C or $Pd(OH)_2/C$ was found to be almost completely ineffective for this coupling (Table 1, Entries 5 and 6). Then, the influence of several parameters such as the base, solvent and temperature with the use of $PdCl(C_3H_5)(dppb)$ as the catalyst was examined. AcOK also led to a high yield of **1** (Table 1, Entry 9). By using carbonates or KF as bases, lower conversions were obtained (Table 1, Entries 10–12). The influence of a few other solvents such as dmf, dmso, nmp, dioxane or xylene was also examined, but in all cases, low conversions were observed (Table 1, Entries 13–17). An elevated reaction temperature (150 °C) was necessary to obtain a high yield of the product. At 130 °C, a lower conversion of 32% was obtained. On the other hand, a very high reaction temperature led to a very low conversion of 6%. This is probably due to faster decomposition of the catalyst (Table 1, Entries 18 and 19).

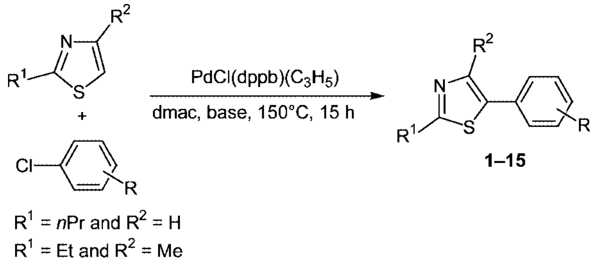
Then, the scope and limitations of this reaction by using $PdCl(dppb)(C_3H_5)$ in dmac with AcOK or AcONa as bases at 150 °C was investigated (Scheme 2, Table 2). The reaction

Table 2. Palladium catalysed cross-coupling with thiazole derivatives (Scheme 2). Conditions: $PdCl(dppb)(C_3H_5)$ see ref.[14], ArCl (1 equiv.), thiazole derivative (2 equiv.), AcOK or AcONa (4 equiv.), dmac, 150 °C, 15 h, GC and NMR yields.

Entry	Thiazole	Aryl chloride	Base	Product	Yield [%][a]
1	2-*n*-propylthiazole	4-chlorobenzaldehyde	AcOK	**2**	89 (74)
2	2-*n*-propylthiazole	methyl 4-chlorobenzoate	AcOK	**3**	85 (72)
3	2-*n*-propylthiazole	4-trifluoromethylchlorobenzene	AcOK	**4**	63 (56)[b]
4	2-*n*-propylthiazole	4-chlorobenzonitrile	AcOK	**5**	84 (75)
5	2-*n*-propylthiazole	4-chloronitrobenzene	AcONa	**6**	55
6	2-*n*-propylthiazole	4-chloronitrobenzene	AcOK	**6**	100 (79)
7	2-*n*-propylthiazole	4-chlorofluorobenzene	AcOK	–	0
8	2-*n*-propylthiazole	3-chlorobenzonitrile	AcOK	**7**	69 (57)
9	2-*n*-propylthiazole	2-chlorobenzaldehyde	AcONa	**8**	85 (63)
10	2-*n*-propylthiazole	2-chlorobenzaldehyde	AcOK	**8**	75
11	2-*n*-propylthiazole	2-trifluoromethylchlorobenzene	AcOK	**9**	13 (11)
12	2-*n*-propylthiazole	2-chlorobenzonitrile	AcOK	**10**	46 (41)
13	2-ethyl-4-methylthiazole	4-chlorobenzonitrile	AcOK	**11**	92 (71)
14	2-ethyl-4-methylthiazole	4-chloronitrobenzene	AcOK	**12**	98 (73)
15	2-ethyl-4-methylthiazole	4-chlorobenzaldehyde	AcOK	**13**	62 (52)
16	2-ethyl-4-methylthiazole	3-chlorobenzonitrile	AcOK	**14**	48 (44)
17	2-ethyl-4-methylthiazole	2-chlorobenzaldehyde	AcOK	**15**	82 (70)

[a] Yields in parenthesis are isolated yields. [b] Reaction performed in an autoclave.

proceeds nicely with several *para*-substituted aryl chlorides. Electron-withdrawing groups in the aryl chlorides are favourable, whereas an electron-donation group is unfavourable. For example, the coupling with 4-chlorobenzaldehyde, methyl 4-chlorobenzoate, 4-chlorobenzonitrile or 4-chloronitrobenzene gave the corresponding 5-aryl-2-*n*-propylthiazoles **2**–**6** in good yields (Table 2, Entries 1–6). On the other hand, poorly activated 4-chlorofluorobenzene was recovered unreacted (Table 2, Entry 7). This result seems to indicate that with this catalyst the oxidative addition of the aryl chloride to palladium is the rate-limiting step of the catalytic cycle. As expected, quite similar reactivity was obtained by using *meta*-substituted 3-chlorobenzonitrile (Table 2, Entry 8). Sterically congested *ortho*-substituted aryl chlorides gave low-to-high yields of **8**–**10**, depending on the substituents (Table 2, Entries 9–12).



Scheme 2.

Finally, the coupling in the presence of the sterically more-hindered 2-ethyl-4-methylthiazole was studied. 2-Ethyl-5-aryl-4-methylthiazole derivatives **11**–**15** were obtained selectively in moderate-to-high yields (Table 2, Entries 13–17).

Conclusions

In the presence 1 mol-% of the air-stable $PdCl(dppb)(C_3H_5)$ complex, the direct arylation of 2-substituted thiazole derivatives with the use of aryl chlorides proceeds in moderate-to-high yields. The structure of the ligand, palladium source and reaction conditions have a large influence on the yields. With this system, only electron-deficient aryl chlorides gave satisfactory results. However, it should be noted that a wide range of functionalities such as acetyl, formyl, ester, nitro, nitrile or trifluoromethyl on the aryl chloride is tolerated. This procedure is very simple, economically attractive and uses commercially available ligand and catalyst precursors. The air-stability of the catalyst and ligand make this procedure more convenient than those using bulky electron-rich phosphanes that are often employed to activate aryl chlorides in palladium-catalysed reactions.[11]

Experimental Section

As a typical experiment, a mixture of 4-chloroacetophenone (0.154 g, 1 mmol), 2-*n*-propylthiazole (0.254 g, 2 mmol) and AcOK (0.392 g, 4 mmol) was heated at 150 °C for 15 h in dry dmac (5 mL) in the presence of $PdCl(dppb)(C_3H_5)$[14] (6.1 mg, 0.01 mmol) under an atmosphere of argon. After extraction with dichloromethane, evaporation and filtration through silica gel (pentane/ether) corresponding product **1** was obtained in 53% (0.129 g) isolated yield as an oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.5 Hz, 2 H), 7.92 (s, 1 H), 7.60 (d, J = 8.5 Hz, 2 H), 2.99 (t, J = 7.4 Hz, 2 H), 2.60 (s, 3 H), 1.85 (sext., J = 7.4 Hz, 2 H), 1.03 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.1, 172.1, 138.9, 137.1, 136.2, 136.1, 129.1, 126.3, 35.6, 26.6, 23.3, 13.6 ppm. $C_{11}H_9NOS$ (203.12): C 65.00, H 4.46; found C 64.75, H 4.76.

Supporting Information (see footnote on the first page of this article): Experimental details for the preparation of the Pd catalyst and compounds **2**–**15**.

Acknowledgments

A. G. is grateful to EGIDE for a grant. We thank the Centre National de la Recherche Scientifique for providing financial support.

---

[1] J. J. Li, G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon, Amsterdam, **2000**.

[2] For selected examples of palladium cross-coupling reactions of thiazoles by Suzuki coupling, see: a) P. Vachal, L. M. Toth, *Tetrahedron Lett.* **2004**, *45*, 7157; b) K. J. Hodgetts, M. T. Kershaw, *Org. Lett.* **2002**, *4*, 1363.

[3] For selected examples of palladium cross-coupling reactions of thiazoles by Stille coupling, see: a) R. Benhida, F. Lecubin, J.-L. Fourrey, L. R. Castellanos, L. Quintero, *Tetrahedron Lett.* **1999**, *40*, 5701; b) D. Guianvarc'h, J.-L. Fourrey, R. Maurisse, J.-S. Sun, R. Benhida, *Org. Lett.* **2002**, *4*, 4209; c) P. Stanetty, M. Schnürch, M. D. Mihovilovic, *J. Org. Chem.* **2006**, *71*, 3754.

[4] For selected examples of palladium cross-coupling reactions of thiazoles by Negishi coupling, see: a) J. Jensen, N. Skjaerbaek, P. Vedsø, *Synthesis* **2001**, 128; b) O. Hara, T. Nakamura, F. Sato, K. Makino, Y. Hamada, *Heterocycles* **2006**, *68*, 1.

[5] For reviews on palladium-catalysed C-H bond activation of heteroaryls, see: a) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731; b) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; c) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200.

[6] For examples of direct 5-arylation of thiazoles by using aryl bromides, see: a) A. Yokooji, T. Okazawa, T. Satoh, M. Miura, M. Nomura, *Tetrahedron* **2003**, *59*, 5685; b) A. Mori, A. Sekiguchi, K. Masui, T. Shimada, M. Horie, K. Osakada, M. Kawamoto, T. Ikeda, *J. Am. Chem. Soc.* **2003**, *125*, 1700; c) M. Parisien, D. Valette, K. Fagnou, *J. Org. Chem.* **2005**, *70*, 7578.

[7] For examples of direct 5-arylation of thiazoles by using aryl iodides, see: a) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467; b) Y. Kondo, T. Komine, T. Sakamoto, *Org. Lett.* **2000**, *2*, 3111; c) K. Masui, A. Mori, K. Okano, K. Takamura, M. Kinoshita, T. Ikeda, *Org. Lett.* **2004**, *6*, 2011; d) A. Mori, A. Sekiguchi, K. Masui, T. Shimada, K. Kobayashi, M. S. M. Ahmed, A. Mori, *Tetrahedron* **2006**, *62*, 9548.

[8] For examples of intramolecular direct arylation of heteroaromatics by using aryl chlorides, see: a) M. Smet, J. Van Dijk, W. Dehaen, *Synlett* **1999**, 495; b) T. H. M. Jonckers, B. U. W. Maes, G. L. F. Lemière, G. Rombouts, L. Pieters, A. Haemers, R. A. Dommisse, *Synlett* **2003**, *5*, 615; c) J.-P. Leclerc, M. André, K. Fagnou, *J. Org. Chem.* **2006**, *71*, 1711.

[9] For examples of bimolecular direct arylation of heteroaromatics by using aryl chlorides, see: a) K. J. Hodgetts, M. T. Kershaw, *Org. Lett.* **2003**, *5*, 2911; b) J.-P. Leclerc, K. Fagnou, *Angew. Chem. Int. Ed.* **2006**, *45*, 7781.

[10] Y. Aoyagi, A. Inoue, I. Koizumi, R. Hashimoto, K. Tokunaga, K. Gohma, J. Komatsu, K. Sekine, A. Miyafuji, J. Kunoh, R. Honma, Y. Akita, A. Ohta, *Heterocycles* **1992**, *33*, 257.
[11] a) A. Littke, G. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; b) H. A. Chiong, O. Daugulis, *Org. Lett.* **2007**, *9*, 1449.
[12] L. Ackermann, *Org. Lett.* **2005**, *7*, 3123.
[13] A. Battace, M. Lemhadri, T. Zair, H. Doucet, M. Santelli, *Organometallics* **2007**, *26*, 472.
[14] T. Cantat, E. Génin, C. Giroud, G. Meyer, A. Jutand, *J. Organomet. Chem.* **2003**, *687*, 365.

Received: April 18, 2007