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Palladium-catalyzed amidation of 2-chloropyrimidines

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ABSTRACT

A mild and efficient Pd-catalyzed coupling of amides with 2-chloropyrimidines is described. The use of bidentate phosphines, such as Xantphos (**7**), as supporting ligands was found to be crucial for providing high yields of 2-(*N*-acylamino)pyrimidine coupling products **1**.

The Pd-catalyzed cross-coupling of amides with aryl halides has emerged as a powerful method for the construction of (*N*-acylamino)arenes.[1] Efficient couplings of both primary and secondary amides with various aryl halides[2] and sulfonates[3] have been reported. In the course of our medicinal chemistry efforts, we required access to substituted 2-(*N*-acylamino)pyrimidines **1** (Fig. 1). However, to our knowledge, there have been no reports of C–N cross-coupling reactions between amides and 2-halopyrimidines.[4] Inspired by the broad functional group tolerance and robust nature of Pd-catalyzed processes, we set out to develop a related protocol for the synthesis of diverse pyrimidines **1**. In this Letter, we describe a method for the N-arylation of amides with 2-chloropyrimidines using a Pd catalyst derived from the bidentate phosphine ligand Xantphos (**7**) (Fig. 1).

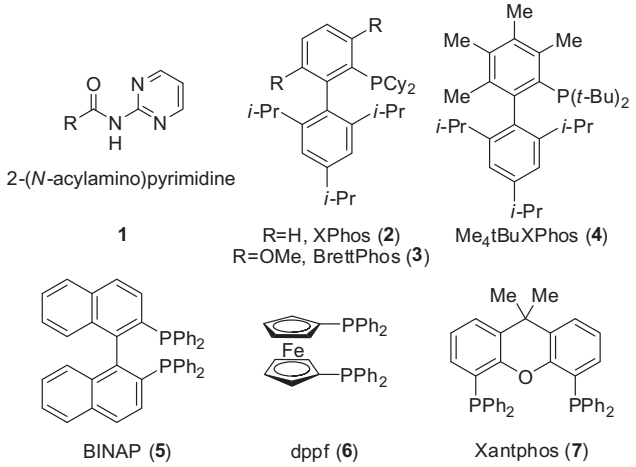
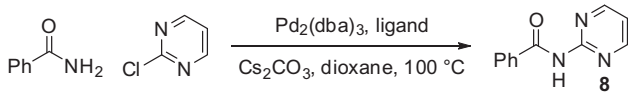


Figure 1. 2-(*N*-Acylamino)pyrimidine architecture and phosphine ligands.

Table 1
The effect of ligand on the Pd-catalyzed amidation of 2-chloropyrimidine



Entry[a]	Ligand	$Pd_2(dba)_3$ (%)	Yield[b] (%)
1	None	0	2
2	None	5	2
3	XPhos (**2**)	5	29
4	XPhos (**2**)	5	43[c]
5	BrettPhos (**3**)	5	35
6	Me_4tBuXPhos (**4**)	5	3
7	Me_4tBuXPhos (**4**)	5	41[d]
8	BINAP (**5**)	5	89
9	dppf (**6**)	5	89
10	dppf (**6**)	5	92[c]
11	Xantphos (**7**)	5	94
12	Xantphos (**7**)	5	91[c]
13	Xantphos (**7**)	1	82

[a] Reaction conditions: 2-chloropyrimidine (1.2 equiv), benzamide (1 equiv), $Pd_2(dba)_3$ (5 mol % or as otherwise indicated), ligand (1.5 equiv to Pd), Cs_2CO_3 (1.4 equiv), 1,4-dioxane (0.5 M), 100 °C.
[b] Yields refer to pure isolated product after a reaction time of 16 h and are unoptimized.
[c] Toluene and 110 °C were used instead of dioxane and 100 °C, respectively.
[d] K_3PO_4 and *t*-BuOH was used instead of Cs_2CO_3 and dioxane, respectively.

In our initial studies, we sought to define suitable conditions for the Pd-catalyzed coupling of benzamide with 2-chloropyrimidine (Table 1). Recently, Buchwald and co-workers have demonstrated the utility of monodentate biaryl phosphine ligands, such as XPhos (**2**), BrettPhos (**3**), and Me_4tBuXPhos (**4**) (Fig. 1), in the Pd-catalyzed amidation of aryl halides and sulfonates.[2b–e,3b–e] Unfortunately, in our hands, Pd catalysts derived from these ligands performed poorly in the amidation of 2-chloropyrimidine (entries 3, 5, and 6). Given this surprising result, we hypothesized that the amidation product **8** may be interfering with catalyst turnover by promoting the formation of an inactive Pd-chelate complex. We, therefore, surmised that switching to bidentate phosphine ligands would prove beneficial. To our delight, Pd catalysts derived from

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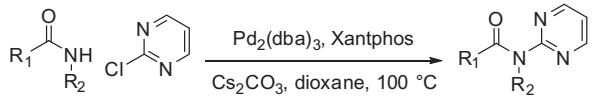
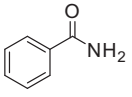
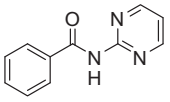
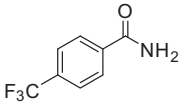
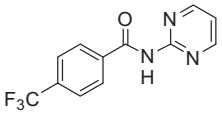
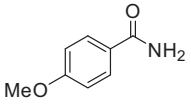
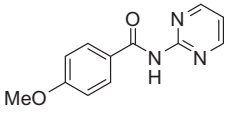
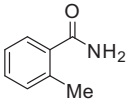
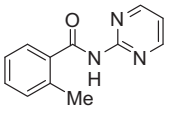
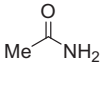
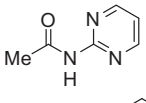
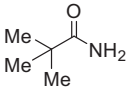
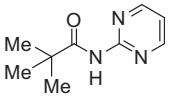
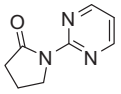
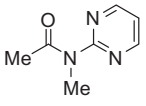
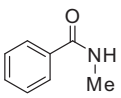
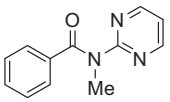
several bidentate phosphines, including BINAP (**5**), dppf (**6**), and Xantphos (**7**), all afforded excellent yields of the coupled product **8** (entries 8, 9, and 11).[5,6] Xantphos (**7**), in particular, has been widely employed as a supporting ligand in Pd-catalyzed amidation reactions[2a,3a,3h,7] and, on this basis, was chosen for further evaluation in this process.

We next examined the scope of the amide component in the Pd-catalyzed amidation of 2-chloropyrimidine (Table 2). A variety of amides, including aromatic, aliphatic, and cyclic derivatives, participated in the coupling reaction. Notably, electron-rich, electron-deficient, and *ortho*-substituted benzamides all coupled efficiently (entries 2–4). Considerable variation in the steric requirement of primary aliphatic amides was readily accommodated (entries 5 and 6). In fact, coupling of the sterically encumbered substrate pivalamide furnished the expected acylaminopyrimidine in nearly quantitative yield (entry 6). A cyclic secondary amide (or lactam) also reacted efficiently (entry 7). However, in accordance with previous disclosures, acyclic secondary amides proved to be reluctant coupling partners (entries 8 and 9).[2a]

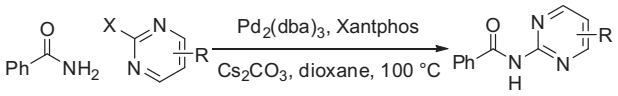
Table 2
The Pd-catalyzed coupling of 2-chloropyrimidine with representative amides

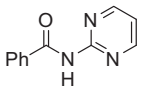
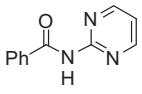
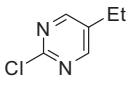
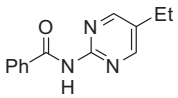
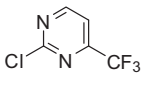
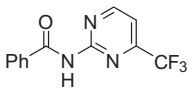
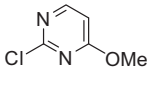
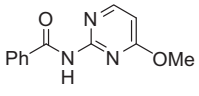
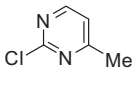
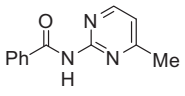


Entry[a]	Amide	Product	Yield[b] (%)
1			94
2			71
3			87
4			80
5			91
6			96
7			93
8			38
9			32

[a] Reaction conditions: ArCl (1.2 equiv), amide (1 equiv), $Pd_2(dba)_3$ (5 mol %), Xantphos (15 mol %), Cs_2CO_3 (1.4 equiv), 1,4-dioxane (0.5 M), 100 °C.
[b] Yields refer to pure isolated product after a reaction time of 16 h and are unoptimized.

Table 3
The Pd-catalyzed coupling of benzamide with representative halopyrimidines



Entry[a]	Azine	Product	Yield[b] (%)
1			94
2			71
3			65
4			96
5			82
6			27

[a] Reaction conditions: ArX (1.2 equiv), amide (1 equiv), $Pd_2(dba)_3$ (5 mol %), Xantphos (15 mol %), Cs_2CO_3 (1.4 equiv), 1,4-dioxane (0.5 M), 100 °C.
[b] Yields refer to pure isolated product after a reaction time of 16 h and are unoptimized.

Significant variation in the halopyrimidine component of the amidation reaction was also permitted (Table 3). Both 2-chloro- and 2-bromopyrimidine were suitable substrates for amidation with benzamide (entries 1 and 2). In general, substitution of the halopyrimidine nucleus with electron-withdrawing or electron-donating functional groups did not appreciably alter the efficiency of the reaction (entries 3–5). It is worth noting, however, that couplings of 2-chloro-4-methylpyrimidine (entry 6) and 2-chloro-4,6-dimethylpyrimidine (not shown) did not proceed to full conversion. We suspect that the poor reactivity of chloropyrimidines bearing methyl substituents at the 4- or 6-positions may be attributable to the relative acidity of the conjugated pseudo-benzylic protons.

In conclusion, we have described a mild and efficient Pd-catalyzed coupling of amides with 2-chloropyrimidines for the formation of diverse 2-(*N*-acylamino)pyrimidines **1**. The use of bidentate phosphines, such as Xantphos (**7**), as supporting ligands was found to be important for achieving high yields of coupled products. Studies to evaluate the scope of 2-haloazine component of the amidation reaction are underway.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.088.

References and notes

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3. (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043; (b) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653; (c) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754; (d) Dooleweerdt, K.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2010**, *12*, 2350; (e) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Synthesis* **2005**, 3229; (f) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777; (g) Klapars, A.; Campos, K. R.; Chen, C.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185; (h) Imbriglio, J. E.; DiRocco, D.; Raghavan, S.; Ball, R. G.; Tsou, N.; Mosley, R. T.; Tata, J. R.; Colletti, S. *Tetrahedron Lett.* **2008**, *49*, 4897.

4. Example of amidation of 2-chloropyridopyrimidines and 3-chloropurine, respectively: (a) Tikad, A.; Routier, S.; Akssira, M.; Leger, J.; Jarry, C.; Guillaumet, G. *Synthesis* **2009**, *14*, 2379; (b) Vilarrasa, J.; Caner, J. *J. Org. Chem.* **2010**, *75*, 4880.

5. *Typical procedure for Pd-catalyzed amidation of 2-chloropyrimidines*. A screw-cap vial was charged with benzamide (121 mg, 1.00 mmol), Cs_2CO_3 (456 mg, 1.40 mmol), Xantphos (87 mg, 0.15 mmol), $Pd_2(dba)_3$ (46 mg, 0.050 mmol), 2-chloropyrimidine (137 mg, 1.20 mmol), and 1,4-dioxane (2 mL). The mixture was sparged with nitrogen for 3 min, stirred for 16 h at 100 °C, and cooled to room temperature. The residue was diluted with dichloromethane, filtered through celite, and concentrated. The crude product was purified by silica gel flash chromatography (40–100% ethylacetate/hexanes) to provide *N*-(pyrimidin-2-yl)benzamide (188 mg, 0.85 mmol, 94% yield) as an amorphous solid (Table 1, entry 8).

6. The reaction efficiency observed with dppf (**6**) as a supporting ligand and toluene as solvent (Table 1, entry 10) is in discord with results disclosed in Ref. 4b pertaining to the amidation of a 3-chloropurine derivative (0% yield). The disparity between these two results accentuates the reactivity variation often observed among differing heterocyclic architectures.

7. Example of amidation of 2-iodopurines: (a) Vandromme, L.; Legraverend, M.; Kreimerman, S.; Lozach, O.; Meijer, L.; Grierson, D. S. *Bioorg. Med. Chem.* **2007**, *15*, 130; (b) Piguel, S.; Legraverend, M. *J. Org. Chem.* **2007**, *72*, 7026.