Amination of heteroaryl chlorides: palladium catalysis or S_NAr in green solvents?

Katie Walsh,[a] Helen F. Sneddon[b] and Christopher J. Moody*[a]

[a] Ms. K. Walsh, Prof Dr C. J. Moody, School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, U.K. Fax: (+) 44 115 951 3564 E-mail: c.j.moody@nottingham.ac.uk

[b] Dr H. F. Sneddon, Green Chemistry Performance Unit, GlaxoSmithKline R&D Ltd, Medicines Research Centre, Stevenage, Hertfordshire SG1 2NY, U.K.

Abstract: Reaction of heteroaryl chlorides in the pyrimidine, pyrazine and quinazoline series with amines in water in the presence of KF results in a facile S_NAr reaction and *N*-arylation. The reaction is less satisfactory with pyridines unless an additional electron withdrawing group is present. The results showed that transition-metal-free S_NAr compares favourably to palladium catalysed coupling reactions, but also operates under environmentally acceptable ("green") conditions in terms of the base and solvent.

Keywords: amination • aromatic substitution • nucleophilic substitution • green chemistry

Introduction

The formation of aryl C-N bonds is a fundamental process within organic chemistry, and the product *N*-aryl-amines are present in a wide variety of natural products and pharmaceutical molecules.[1] Examples include the well known, clinically used kinase inhibitors imatinib and gefitinib (Figure 1). Recent analyses showed heteroatom alkylations and arylations to be the largest single class of transformations used in medicinal chemistry, and heteroaryl *N*-arylations make up a very significant subclass of these transformations.[2, 3] Traditionally, these structures have been accessed through nucleophilic aromatic substitution (S_NAr) reactions on appropriately activated substrates,[4] although poor substrate scope and

reactivity are major limitations to this method. Alternatively, the copper-mediated amination of halobenzenes, discovered by Ullmann in 1903 and shown to be catalytic by Goldberg three years later, can also be used for the synthesis of a range of *N*-aryl compounds, and although the original methodology had limitations, recent developments have resulted in substantial improvements.[5] However the most significant breakthrough in this arena came in 1994 when Buchwald and Hartwig independently developed a palladium-catalysed *N*-arylation reaction.[6, 7] With its improved substrate scope and functional group tolerance, the Buchwald-Hartwig amination has become a fundamental part of modern organic chemistry.[8]

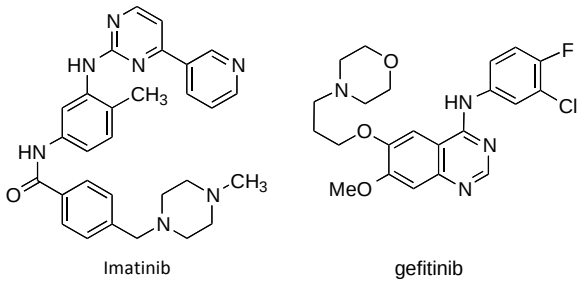
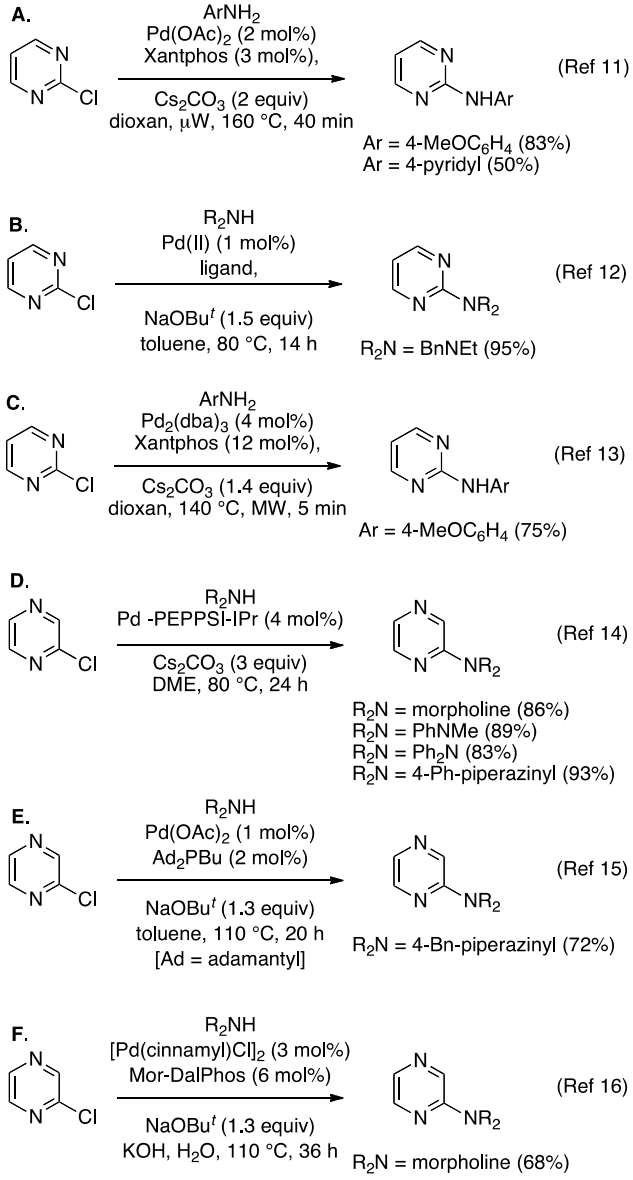


Figure 1.

However, precious metals are an expensive and dwindling resources, and whilst the success of Pd-catalysed reactions has undoubtedly revolutionalised *N*-arylation chemistry, there is a risk that they are used without due consideration of alternatives. For instance, 2-chloropyrimidine is 10^{14} - 10^{16} times more reactive than chlorobenzene in terms of its ability to undergo S_NAr reactions,[9, 10] but examination of the recent literature reveals that even such reactive substrates are being subjected to Pd-catalysed amination reactions. Some recent examples of Pd-catalysed amination of 2-chloropyrimidine and chloropyrazine are shown in Scheme 1,[11-16] and whilst these reactions, some of which are carried out under fairly forcing conditions with non-trivial ligands, clearly proceed in good yield, it does beg the question as to whether the palladium is really needed for such highly activated substrates. Indeed, the literature contains many examples of activated heteroaromatic chlorides reacting readily under S_NAr conditions, so the fact that such processes appear to have been sidelined in favour of their Pd-mediated counterparts puzzled us.

Consequently, we sought to optimise the coupling of heteroaromatic chlorides with amine nucleophiles under S_NAr conditions with a view to defining parameters that not only gave comparable yields to the published Pd-catalysed methods, but also operated under environmentally acceptable conditions in terms of the base and solvent. We now report the results of this detailed study.



Scheme 1. Examples of palladium catalysed amination of reactive heteroaryl chlorides.

Results and Discussion

The reaction of chloropyrazine with a secondary amine morpholine to give morpholinopyrazine **1** was taken as a simple test reaction to screen a range of solvents and bases, although from the outset we limited

ourselves to solvents that are generally accepted as 'green'.[17] Solvents with environmental or toxicity alerts were disregarded, and as a result of previous literature,[11, 14] caesium carbonate was initially chosen as the base for these reactions. Although caesium carbonate is acknowledged sometimes to create problematic waste streams on scale, its solubility made it a good starting point for these studies. Organic solvents were found to be generally ineffective for reactions of chloropyrazine (Table 1, Entries 1-6), although somewhat better in the reaction of 2-chloropyrimidine to give 2-morpholinopyrimidine **2** (data shown in Supporting Information). However, for both the chloro-heterocycles, the best result was obtained using water as solvent, giving both the highest yield and the cleanest reaction mixtures, in most cases the product requiring just a simple extraction with isopropyl acetate. Since the reaction mixture is not homogeneous, this unexpected result might be attributed to an "on-water" effect.[18] Yields were further improved from 33% to 58% (Table 1, Entry 6) by raising the temperature to 100 °C. Water is not, automatically, a green solvent. For any given reaction, consideration needs to be given to how the waste water is to be handled, whether it is energy intensive to clean, or whether contaminated aqueous streams have to be incinerated where other waste solvent streams could be recycled or productively burnt to generate heat and power. However, when multiple factors are weighed,[17] water is often one of the more benign choices. Isopropyl acetate was chosen for extractions, mindful that this can be easier to recover and recycle on scale than ethyl acetate.

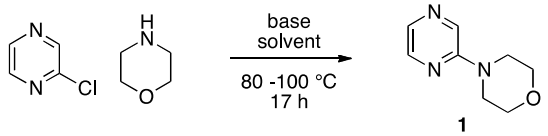


Table 1. Reaction of 2-chloropyrazine with morpholine with various solvents and bases.[a]

Entry	Base	Solvent	Yield/%
1	Cs_2CO_3	2-Me-THF	3
2	Cs_2CO_3	2-Me-THF/H_2O (1:1)	18
3	Cs_2CO_3	1-butanol	<5

4	Cs_2CO_3	EtOAc	4
5	Cs_2CO_3	H_2O	33[b]
6	Cs_2CO_3	H_2O	58
7	DBU	H_2O	40[b]
8	Et_3N	H_2O	38
9	K_2CO_3	H_2O	63
10	$CaCO_3$	H_2O	38
11	K_3PO_4	H_2O	60
12	KF	H_2O	70
13	KF[c]	H_2O	30
14	KF[d]	H_2O	64[b]
15	KF	H_2O	47[b]
16	KF	H_2O	63[e]
17	KF	H_2O	81[c,f]

[a] All reactions were performed with chloropyrazine (1 eq.), morpholine (1 eq.) and base (2 eq.) in the specified solvent at 80 °C for 17 h. Reactions in water were carried out at 100 °C unless otherwise specified; [b]The reaction was performed at 80 °C; [c]The reaction used 1 eq. of base; [d]The reaction used 3 eq. of base; [e]The reaction was carried out in a microwave reactor (300 W) at 150 °C for 30 min; [f]The reaction was carried out in a microwave reactor (300 W) at 175 °C for 30 min.

We then investigated the reactions with chloropyrazine with morpholine in water with respect to the base (Table 1, Entries 7-15). Organic bases proved inefficient in water (Entries 7, 8), and moderate yields were achieved using other carbonates or potassium phosphate bases (Entries 9-11). Potassium fluoride was found to be the most effective base and as a result was investigated further. Reducing the amount of base to one equiv dramatically lowered the yield (Entry 13), but only a small increase in yield was observed when increasing to three equivalents (Entry 14). However it was found that with two equivalents of

potassium fluoride in water at reflux (Entry 12) the highest yield of 70% of morpholinopyrazine **1** was achieved. Reaction times are shortened dramatically by conducting the reaction in a microwave reactor for 30 min at 150 or 175 °C (63 and 81% yield respectively). ICP-MS analysis was performed to determine what levels of other metals were present in the sample of potassium fluoride. Copper could not be detected at a limit of 24 ppb and palladium was not detected at a limit of 10 ppb.

These results stand favourable comparison with the Pd-catalysed variants that give morpholinopyrazine **1** in 86% yield using Pd-PEPPSI, Cs_2CO_3 in DME at 80 °C (Scheme 1D),[14] or in 68% yield using $[Pd(cinnamyl)Cl]_2$, Mor-DalPhos, $NaOBu^t$, KOH, H_2O at 110 °C (Scheme 1E).[16] On the other hand, other workers have also found that the palladium catalyst is unnecessary, the reaction of chloropyrazine with morpholine proceeding at 130 °C in DMSO.[19]

With the useful KF in water conditions now established, chloropyrazine and 2-chloropyrimidine were screened against a wide range of primary and secondary amines, as well as anilines and NH heteroaromatic compounds, selected to contain a range of functional groups of relevance to contemporary medicinal chemistry, to give the corresponding *N*-arylamines **1**-**23** (Table 2). As expected, reactions with the more reactive 2-chloropyrimidine generally gave higher yields (2-chloropyrimidine is *ca*. 100 times more reactive than chloropyrazine),[9] and reacted in moderate to excellent yield with primary and secondary amines (Table 2, Entries 1-11), and in the case of α-methylbenzylamine (Entry 5) HPLC showed there was no loss of enantiomeric excess in the final product (ee > 98). With *p*-anisidine (Entry 12) the yield of 86% was comparable with the corresponding palladium-catalysed amination [$Pd(OAc)_2$, xantphos, dioxan, microwave, 160 °C, 83%] (Scheme 1A).[11] However, the reaction was poor with *ortho*-substituted anilines and 2-aminothiazole did not react. Chloropyrazine gave moderate to excellent yields with electron-rich primary and secondary amines, but was unreactive with all the anilines and N-H heterocycles examined. Again reaction times can be shortened by conducting the reaction in a microwave

reactor for 60 min at 175 °C (Entries 1 and 4). The structures of the products **1-23** of amination of chloropyrazine and 2-chloropyrimidine with the range of amines are shown in Figure 2.

Where direct comparison is possible, our amination procedure involving KF in water stand comparison with the Pd-catalysed protocols outlined in Scheme 1 (Table 2, Entries 6, 10-12) – 80 vs. 95%, 70 vs. 68 or 86%, 81 vs. 93% and 86 vs. 75 or 83%. In addition, the coupling of 2-chloropyrimidine with imidazole and benzimidazole has been carried out under copper catalysis in 90 and 100% yield respectively,[20] compared with the slightly poorer yields of 62 and 83% under our conditions (Table 2, Entries 14, 15). In other cases, the transition-metal catalyst is clearly beneficial. Whereas chloropyrazine does not readily react with 4-methoxyaniline under our S_NAr conditions (Table 2, Entry 12), palladium catalysis with the BrettPhos ligand results in a high yield of coupled product.[21] Given the high reactivity of 2-chloropyrimidine towards nucleophilic attack, it is not surprising that there are other examples of S_NAr process involving amine nucleophiles (pyrrolidine,[22] cyclohexylamine and 4-methoxybenzylamine[13]), that taken with our own results, reinforce the idea that precious metal catalysis is not need fro amination reactions with such highly activated heteroaryl halides.

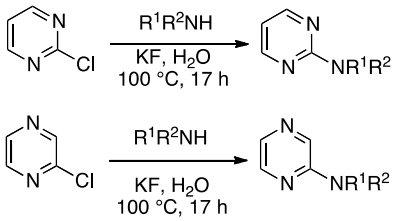
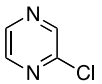
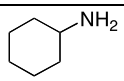
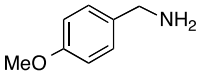
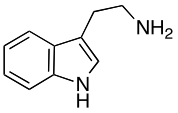
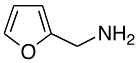
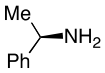
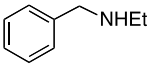
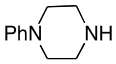
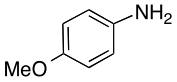
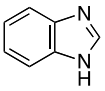
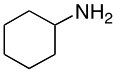


Table 2. Amination of chloropyrazine and 2-chloropyrimidine.[a]

Entry	Amine	Reaction with  Product (Yield)[b,c]	Reaction with  Product (Yield)[b]
1		**3** (28%)	**11** (77%)

		MW 60%	
2		**4** (47%)	**12** (85%)
3		**5** (58%)	**13** (85%)
4		**6** (33%) MW 52%	**14** (81%)
5		-	**15** (78%)
6		-	**16** (80%) [95%]
7		**7** (48%)	**17** (52%)
8		**8** (76%)	**18** (76%)
9		**9** (52%)	**19** (69%)
10		**1** (70%) [68%, 86%]	**2** (84%)
11		**10** (81%[d]) [93%]	**20** (93%)
12		No reaction	**21** (86%) [75%, 83%]
14		No reaction	**22** (62%)
15		No reaction	**23** (83%)
1		**3** (28%) MW 60%	**11** (77%)

[a] [a]All reactions were performed using heteroaryl halide (1 eq.), amine (1 eq.) and KF (2 eq.), in water at 100 °C for 17 h; [b]Yields in square brackets refer to the Pd-catalysed variants shown in Scheme 1; [c]MW

refers to the yield when the reaction was carried out in a microwave reactor (300 W) at 175 °C for 60 min with KF (1 eq.); [d] Yield reported as an NMR yield calculated from internal standard using 1,4-dioxane.

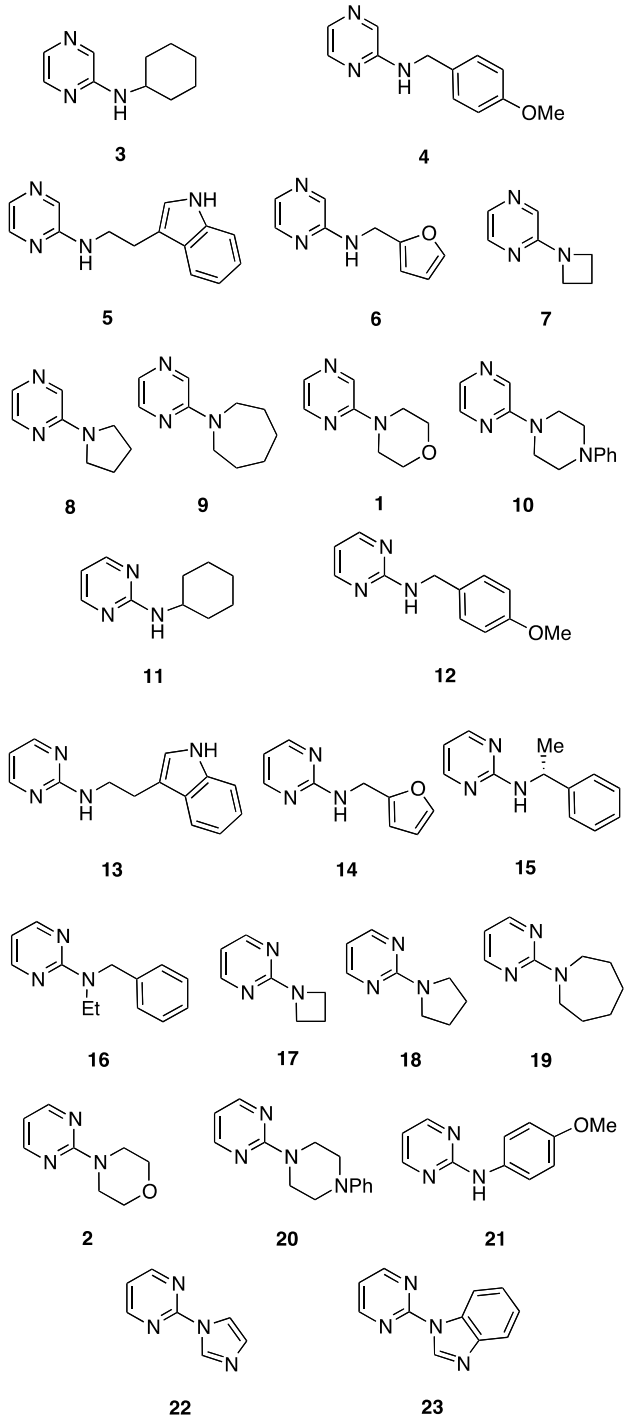


Figure 2. Amination products of chloropyrazine and 2-chloropyrimidine.

From this list of amines, seven represent examples were chosen to be tested against other pyrimidines in comparison with 2-chloropyrimidine itself (Table 3). Unsurprisingly 2-bromopyrimidine showed similar

reactivity, but the reactions with 4-chloro-2,6-diaminopyrimidine were somewhat unpredictable yields, possibly as a result of solubility issues. 4-Chloroquinazoline gave good to excellent yields in all cases, in line with its well known reactivity in S_NAr reactions, for example in the synthesis of 4-anilinoquinazolines as kinase inhibitors.[23] The structures of the new products **24**-**33** obtained are shown in Figure 3.

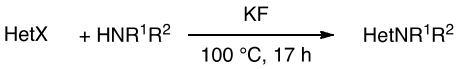
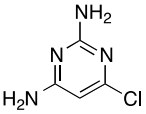
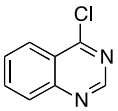
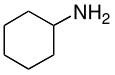
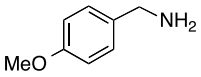
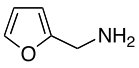
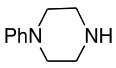
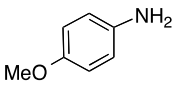


Table 3. Amination of halopyrimidines and 4-chloroquinazoline.[a]

Entry	Amine	Reaction with  Product (Yield)	Reaction with  Product (Yield)	Reaction with  Product (Yield)	Reaction with  Product (Yield)
1		**11** (77%)	**11** (72%)	No reaction	**27** (78%)
2		**12** (85%)	**12** (89%)	No reaction	**28** (71%)
3		**14** (81%)	**14** (68%)	No reaction	**29** (71%)
4		**18** (76%)	**18** (59%)	**24** (45%)	**30** (97%)
5		**2** (84%)	**2** (85%)	**25** (49%)	**31** (80%)
6		**20** (93%)	**20** (91%)	**26** (80%)	**32** (82%)
7		**21** (86%)	**21** (65%)	No reaction	**33** (86%)

[a]All reactions were performed using aryl halide (1 eq.), amine (1 eq.) and KF (2 eq.) in water at 100 °C for 17 h.

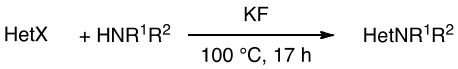
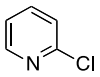
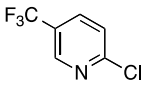
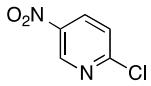
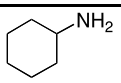
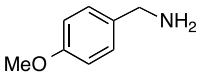
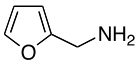
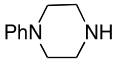
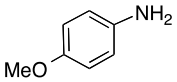


Table 4. Amination of 2-halopyridines.[a]

Entry	Amine	Reaction with  Product (Yield)[b]	Reaction with  Product (Yield)	Reaction with  Product (Yield)[b]	Reaction with  Product (Yield)
1		(<5%)	(6%)	**37** (60%)	**43** (96%)
2		(<5%)	No reaction	**38** (65%)	**44** (70%)
3		(<5%)	No reaction	**39** (48%) MW 59%	**45** (73%)
4		**34** (<5%)	**34** (54%)	**40** (53%)	**46** (74%)
5		**35** (9%) MW 25%	**35** (16%)	**41** (36%)	**47** (87%)
6		**36** (21%[d])	**36** (46%[d])	**42** (85%)	**48** (76%)
7		No reaction	No reaction	No reaction	**49** (73%)

[a]All reactions were performed using aryl halide (1 eq.), amine (1 eq.) and KF (2 eq.) in water at 100 °C for 17 h; [b]MW refers to the yield when the reaction was carried out in a microwave reactor (300 W) at 175 °C for 1 h (2 h in case of furfurylamine) with KF (1 eq.); [c]3 eq. of KF was used in this reaction; [d] Yield reported as an NMR yield calculated from internal standard using 1,4-dioxane.

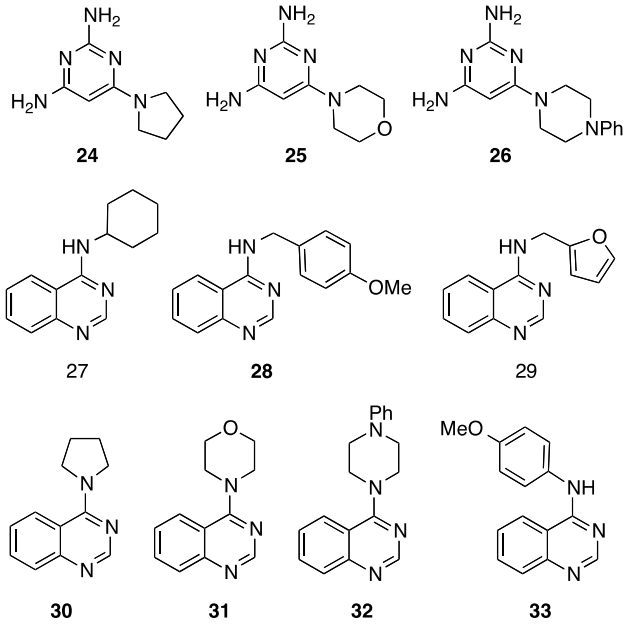


Figure 3. Amination products of halopyrimidines and 4-chloroquinazoline.

The same seven representative amines were also reacted with halopyridines under the KF/water conditions (Table 4), even though 2-chloropyridine is known to be *ca*. 10^8 times less reactive towards nucleophiles than 2-chloropyrimidine under S_NAr conditions. Hence the reactions of the amines with 2-chloroyridine were generally unsatisfactory, although, as expected for an S_NAr reaction, 2-fluoropyridine gave better yields. When the pyridine substrate contained an additional electron-withdrawing group such as trifluoromethyl or nitro, these substituted pyridines demonstrated similar reactivities to the pyrimidines. In particular, 2-chloro-5-nitropyridine gave good results with all the amines examined. The structures of the wide range of *N*-pyridylamines **34**-**49** obtained are shown in Figure 4.

Although 2-bromopyridine is reported to react with pyrrolidine under microwave irradiation,[22] it is clear that in the absence of additional activation, 2-halopyridines represent the limit of what will undergo facile amination reactions under our simple S_NAr conditions. On the other hand, both 2-bromo- and 2-chloro-pyridine undergo coupling under a range of palladium-catalysed conditions with, for example, cyclohexylamine and pyrrolidine,[21] with morpholine,[12, 16] and with 4-methoxyaniline (63%).[24]

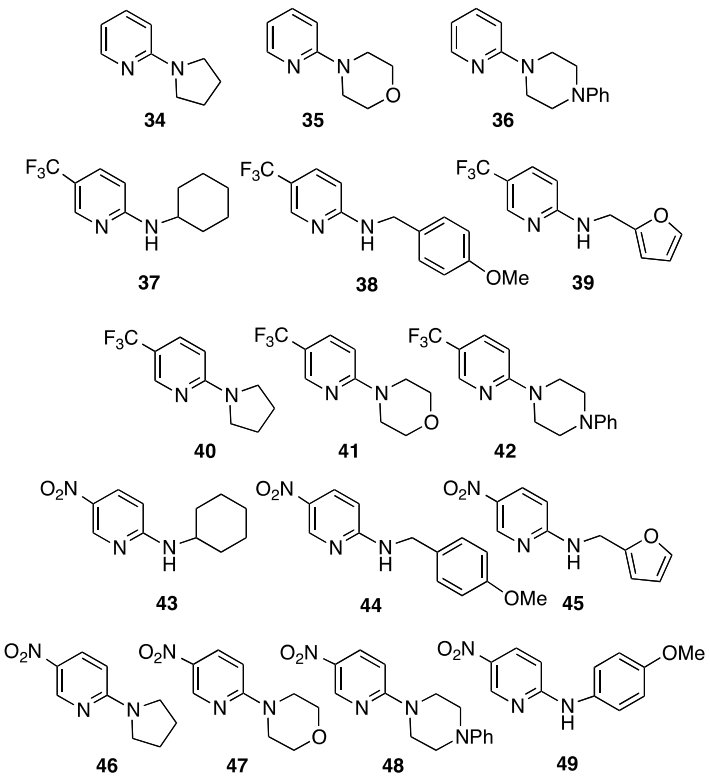


Figure 4. Amination products of 2-halopyridines.

Conclusion

Whilst palladium-catalysed *N*-arylation amination reactions have undoubtedly made a major impact on synthetic organic chemistry, there are examples of reactions involving activated halides, where it might appear that the use of the transition-metal was unnecessary. We have addressed this issue of over-reliance on palladium catalysis in organic chemistry in a range of nucleophilic aromatic substitution reactions with activated heteroaryl halides to synthesise various heteroaryl amine substrates. A set of conditions has been developed using potassium fluoride and water at reflux for 17 h that allow for S_NAr chemistry to be carried out, without the use of palladium catalysis, with a wide range of heteroaryl halides and amines. The results showed that transition-metal-free S_NAr compares favourably to palladium catalysed coupling reactions, but also operated under environmentally acceptable conditions in terms of the base and solvent.

Experimental Section

General Procedure. To a 5 mL Reacti-vial (Thermo Scientific) was added aryl halide (1.75 mmol), amine (1.75 mmol), potassium fluoride (3.50 mmol) in solvent (1 mL) and the resulting mixture heated to 100 °C for 17 h on a heating block. Once cooled, the mixture was quenched with aqueous potassium carbonate solution (40 mL) and extracted into isopropyl acetate (2 × 30 mL). The organic extracts were then combined and washed with brine before being dried over sodium sulfate and the solvent evaporated under reduced pressure. When necessary, purification was carried out by column chromatography over silica gel (light petroleum/ ethyl acetate, 4:1).

Acknowledgements

We thank the Engineering and Physical Sciences Research Council and GlaxoSmithKline for an Industrial CASE award (to K.W.), Matthew Campbell-Crawford (GSK, Stevenage) for some additional experiments, and Ian Churcher, Alan Nadin and Channa Hattotuwagama for helpful discussions about the choice of medicinally relevant amines as coupling partners.

[1] L. Ackermann, in *Modern Arylation Methods* (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**.

[2] J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337-2347.

[3] S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451-3479.

[4] M. B. Smith, J. March, *Advanced Organic Chemistry*, 5th ed., Wiley-Interscience, New York, **2001**.

[5] G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054-3131.

[6] A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1995**, *34*, 1348-1350.

[7] J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609-3612.

[8] D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338-6361.

[9] T. L. Chan, J. Miller, *Aust. J. Chem.* **1967**, *20*, 1595-&.

[10] J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 5th ed., John Wiley & Sons, **2010**.

[11] H. Q. Zhang, Z. Xia, A. Vasudevan, S. W. Djuric, *Tetrahedron Lett.* **2006**, *47*, 4881-4884.

[12] C. V. Reddy, J. V. Kingston, J. G. Verkade, *J. Org. Chem.* **2008**, *73*, 3047-3062.

[13] D. S. Ermolat'ev, E. V. Van der Eycken, *J. Org. Chem.* **2008**, *73*, 6691-6697.

[14] M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443-2452.

[15] D. Michalik, K. Kumar, A. Zapf, A. Tillack, M. Arlt, T. Heinrich, M. Beller, *Tetrahedron Lett.* **2004**, *45*, 2057-2061.

[16] B. J. Tardiff, M. Stradiotto, *Eur. J. Org. Chem.* **2012**, 3972-3977.

[17] R. K. Henderson, C. Jimenez-Gonzalez, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13*, 854-862.

[18] S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279.

[19] A. J. Henderson, M. Hadden, C. Guo, N. Douglas, H. Decornez, M. R. Hellberg, A. Rusinko, M. McLaughlin, N. Sharif, C. Drace, R. Patil, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1137-1140.

[20] Y.-X. Xie, S.-F. Pi, J. Wang, D.-L. Yin, J.-H. Li, *J. Org. Chem.* **2006**, *71*, 8324-8327.

[21] D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 57-68.

[22] S. Narayan, T. Seelhammer, R. E. Gawley, *Tetrahedron Lett.* **2004**, *45*, 757-759.

[23] W. A. Denny, *Farmaco* **2001**, *56*, 51-56.

[24] H. Wang, Y. Wang, C. Peng, J. Zhang, Q. Zhu, *J. Am. Chem. Soc.* **2010**, *132*, 13217-13219.

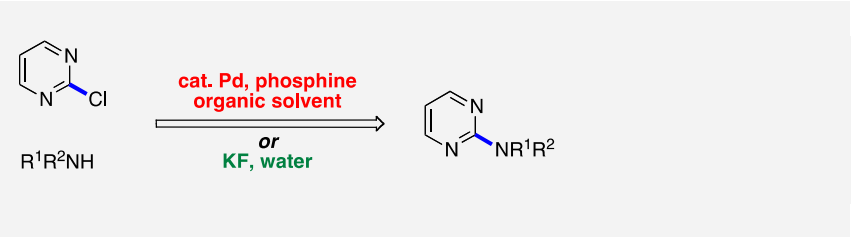
Entry for the Table of Contents (Please choose one layout only)

Layout 2:

Catch Phrase ––––––––––––––––

Katie Walsh, Helen F. Sneddon, and Christopher J. Moody* …….. *Page – Page*

Amination of heteroaryl chlorides: palladium catalysis or S_NAr in green solvents?



Reaction of heteroaryl chlorides with amines using KF in water results in S_NAr reaction and *N*-arylation, as a viable, green alternative to Pd-catalysed amination.