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Palladium-catalysed direct arylations of heteroaromatics using more eco-compatible solvents pentan-1-ol or 3-methylbutan-1-ol

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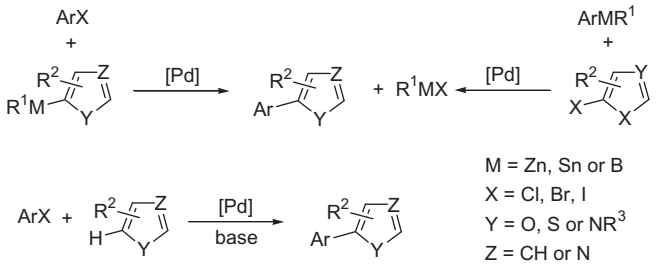
ABSTRACT

The palladium-catalysed direct coupling of aryl halides with heteroaromatics in greener solvents than DMF or DMAc, which are often employed for such couplings, would be a considerable advantage for both industrial application and sustainable development. We observed that a range of aryl bromides undergoe coupling via C–H bond activation/functionalisation reaction of thiazoles or imidazoles in moderate to good yields using pentan-1-ol or 3-methylbutan-1-ol as the solvents. Pentan-1-ol and 3-methylbutan-1-ol are less toxic than DMF or DMAc, moreover they are bioresources as they can be obtained by fermentation. Therefore, these reaction conditions are certainly more eco-compatible than those generally employed for such couplings.

The palladium-catalysed cross-coupling reactions between aryl halides and heteroarenes such as thiophene, pyrroles, furans, imidazoles or thiazoles represent powerful access to arylated heterocycles. Negishi, Stille or Suzuki cross-coupling reactions have been largely employed for the preparation of such compounds (Scheme 1, top).[1] However, these methods are not very convenient as their organometallic derivatives have to be prepared. Moreover, these reactions are not environmentally attractive as they provide an organometal or a salt (MX) as the by-product.

Over the last years, very interesting results for the palladium-catalysed coupling of aryl halides with heteroaromatic derivatives via C–H bond activation have been reported and provide an economical and attractive procedure for the preparation of such compounds (Scheme 1, bottom).[2,3] These coupling reactions provide only HX associated to a base as a by-product and therefore are very interesting both in terms of atom-economy and inert wastes. Despite tremendous improvement of the catalytic efficiency allowing reactions under milder conditions or lower catalyst loadings, this type of transformation still suffers from a major limitation with regard to green chemistry concerning the reaction media since the preferred solvents for these transformations are generally the undesirable and toxic, dimethylformamide (DMF) or dimethylacetamide (DMAc).[2–10] Therefore, the discovery of less toxic solvents for such coupling reactions would be a considerable advantage for sustainable development.



Scheme 1.

Recently, a few 'greener' solvents have been employed for direct arylations. For example, the arylation of oxazoles, thiazoles, indazoles or indoles using water was reported by Greaney, Djakovitch and co-workers.[11] René and Fagnou developed biphasic conditions using water and EtOAc for the direct arylation of thiophenes.[12] Polyethylene glycol (PEG 20000) has been found to be a useful solvent for the direct arylation of triazoles.[13] Carbonates such as diethylcarbonate have also been used successfully for the direct arylation of some heteroaromatics such as oxazole or thiazole derivatives.[14] Finally, the ruthenium-catalysed direct arylation of 2-arylpyridines in carbonates or water has been recently reported by Fischmeister, Dixneuf and co-workers.[15]

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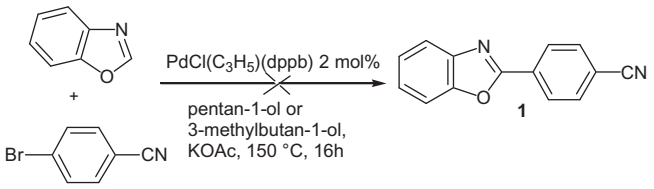
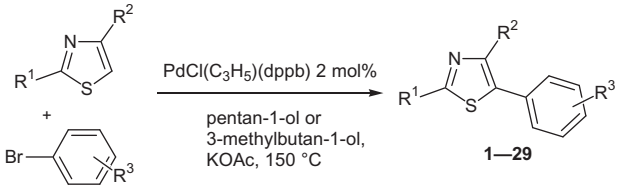


Scheme 2.



Scheme 3.

To our knowledge, so far, alcohols such as pentan-1-ol or 3-methylbutan-1-ol have not been employed as the solvents for palladium-catalysed direct arylations. Pentan-1-ol and 3-methylbutan-1-ol are moderately soluble in water and miscible with common organic solvents. They are not considered a hazardous air pollutant solvent. They are readily biodegradable, unlikely to accumulate in the food chain, and practically non-toxic to fish and aquatic organisms. Pentan-1-ol and 3-methylbutan-1-ol can be prepared by the reduction of 1-valeraldehyde or 3-methylbutyraldehyde (isovaleraldehyde) with hydrogen. They can also be obtained by fermentation and are present in cider, mead, beer, wine, and spirits to varying degrees. They can be isolated by fractional distillation. Overexposure to 1-pentanol or 3-methylbutan-1-ol may cause irritation of the eyes, skin, or respiratory passages; headache, dizziness, coughing, nausea, vomiting or diarrhoea. However, exposure to residual amounts of these alcohols is unlikely to have any adverse health effects, as these alcohols are found as contaminants in some alcoholic beverages such as cider, beer or whisky. Swallowing small amounts of primary

Table 1
Palladium-catalysed 5-arylation of 2-*n*-propylthiazole in pentan-1-ol (Scheme 3)[19,20]

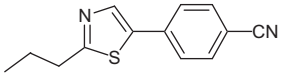
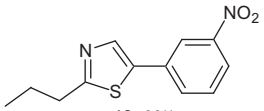
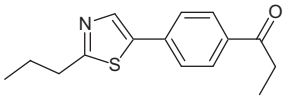
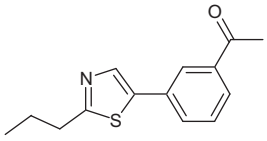
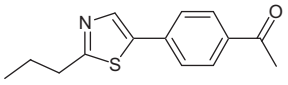
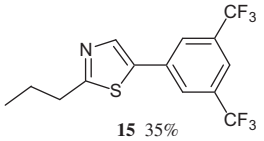
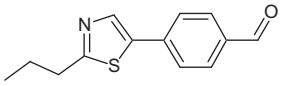
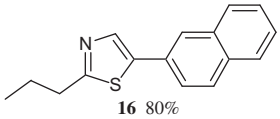
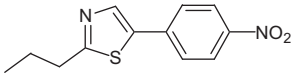
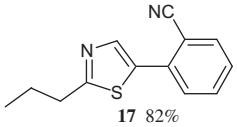
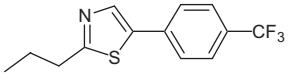
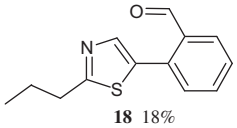
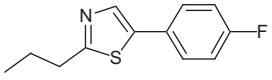
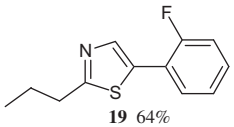
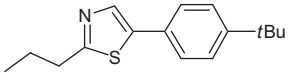
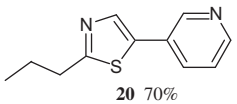
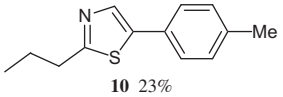
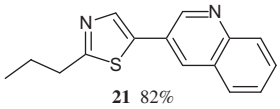
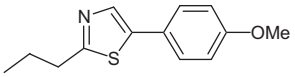
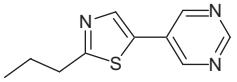
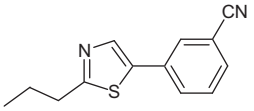
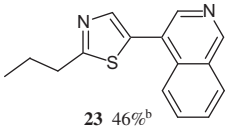
Entry	Product	Entry	Product
1	 **2** 85%	12	 **13** 66%
2	 **3** 67%	13	 **14** 79%
3	 **4** 70%	14	 **15** 35%
4	 5 64%	15	 **16** 80%
5	 **6** 85%	16	 **17** 82%
6	 **7** 50%	17	 **18** 18%
7	 **8** 81%	18	 **19** 64%
8	 **9** 63%	19	 **20** 70%
9	 **10** 23%	20	 **21** 82%

Table 1 (*continued*)

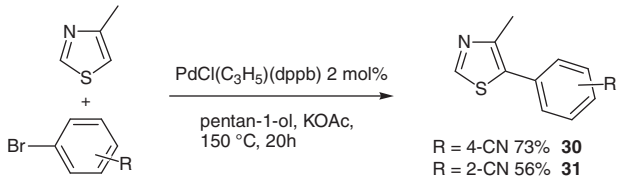
Entry	Product	Entry	Product
10	 **11** 60%	21	 **22** 15%
11	 **12** 78%	22	 **23** 46%[b]

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), aryl bromide (1 mmol), 2-*n*-propylthiazole (2 mmol), KOAc (2 mmol), pentan-1-ol (5 mL), 20 h, 150 °C, isolated yields.
[a] The formation of isoquinoline was also observed.

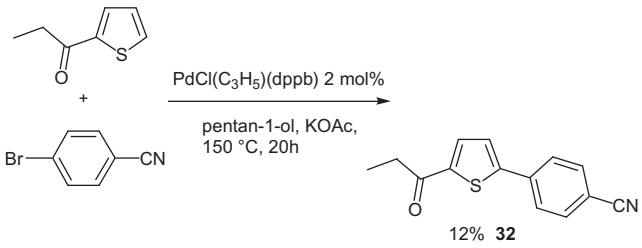
amyl alcohol (an amyl alcohol is any of the 8 alcohols with the formula $C_5H_{11}OH$) incidentally is not likely to cause injury. Therefore, the use of such alcohols as solvents is in agreement with several of the P. Anastas 12 principles of 'green chemistry' including principles 1, 5, 7 and 12.[16]

For this study, both pentan-1-ol and 3-methylbutan-1-ol were employed as the solvents. The reactions were performed under argon in the presence of 2 mol % of $PdCl(C_3H_5)(dppb)$ as the catalyst[17] at 150 °C. First, we examined the coupling of benzoxazole with 4-bromobenzonitrile. We had previously observed that, with this catalyst, this reaction proceeds nicely in DMF or in diethylcarbonate.[14] However, in pentan-1-ol or 3-methylbutan-1-ol, the formation of complex mixtures of products was obtained, and the desired coupling product **1** could not be isolated (Scheme 2).

Then, we examined the reactivity of thiazole derivatives in these solvents. Greaney and co-workers had observed that the direct 5-arylation of thiazoles proceeds nicely 'on water' using 5 mol % $PdCl_2(dppf)$/10 mol % PPh_3 as the catalyst and silver carbonate as the additive.[11a] We had also obtained good results for this reaction in diethylcarbonate.[14b] Employing 2-*n*-propylthiazole and 4-bromobenzonitrile as the coupling partners, at 150 °C for 20 h, in the presence of KOAc as the base and 2 mol % $PdCl(C_3H_5)(dppb)$ as the catalyst in pentan-1-ol, the corresponding 5-arylation product **2** was obtained in good yield (Scheme 3 and Table 1, entry 1). Next, we studied the scope of this reaction. The reaction of other *para*-substituted electron-deficient aryl bromides such as 4-bromopropiophenone, 4-bromoacetophenone, 4-bromobenzaldehyde or 4-bromonitrobenzene with 2-*n*-propylthiazole



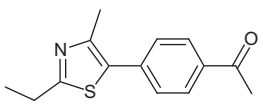
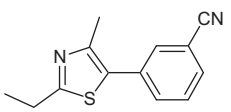
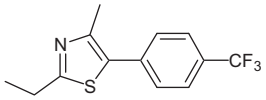
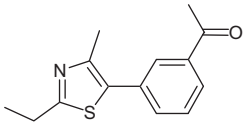
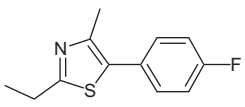
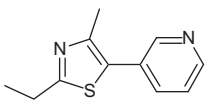
Scheme 4.



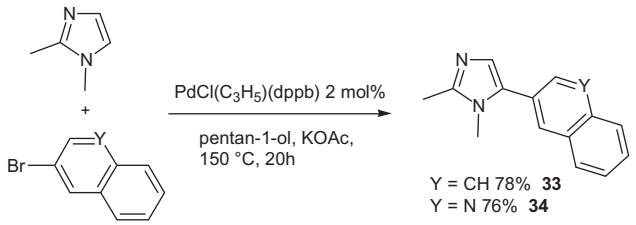
Scheme 5.

gave the expected products **3**–**6** in 64–85% yields (Table 2, entries 2–5). Surprisingly, even deactivated aryl bromides 4-*tert*-butylbromobenzene or 4-bromoanisole gave the desired coupling products **9** and **11** in relatively good yields (Table 1, entries 8 and 10). As expected, the *meta*-substituted aryl bromides,

Table 2
Palladium-catalysed 5-arylation of 2-ethyl-4-methylthiazole in pentan-1-ol (Scheme 3)[19,20]

Entry	Product	Entry	Product
1	 **24** 82%	4	 **27** 75%
2	 **25** 30%	5	 **28** 77%
3	 **26** 67%	6	 **29** 70%

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), aryl bromide (1 mmol), 2-ethyl-4-methylthiazole (2 mmol), KOAc (2 mmol), pentan-1-ol (5 mL), 20 h, 150 °C, isolated yields.



Scheme 6.

3-bromobenzonitrile, 3-bromonitrobenzene or 3-bromoacetophenone, also gave the target compounds **12**–**14** in good yields (Table 2, entries 11–13).

Ortho-substituents on aryl halides generally have a more important influence on the yields of palladium-catalysed reactions due to their steric and/or coordination properties.[18] 2-Bromobenzonitrile and 2-fluorobromobenzene gave **17** and **19** in good yields; whereas a low conversion of the aryl bromide and a poor yield of **18** was obtained when 2-bromobenzaldehyde was employed as the reactant (Table 1, entries 16–18).

Pyridines, quinolines or pyrimidines are among the most common heterocyclic motifs found in pharmaceutically active compounds. Therefore, preparative methods of biheteroaryl derivatives containing such heterocycles remain an essential research topic in organic synthesis. The reaction of 3-bromopyridine or 3-bromoquinoline with 2-*n*-propylthiazole in pentan-1-ol gave the expected coupling products **20** and **21** in 70% and 82% yields, respectively. On the other hand, the use of 5-bromopyrimidine and 4-bromoisoquinoline led to the formation of the 5-arylated thiazoles **22** and **23** in low to moderate yields (Table 1, entries 19–22). In the course of the reaction with 4-bromoisoquinoline, a dehalogenation side-reaction to form isoquinoline was observed.

Then, in order to determine the influence of a 4-substituent on thiazole on the reaction rates using this procedure, 2-ethyl-4-methylthiazole was employed as the reactant (Scheme 3 and Table 2). Five electron-deficient aryl bromides and 3-bromopyridine have been employed, and in most cases the desired products **24**–**29** were formed in good to high yields. Again, the use of 4-trifluoromethylbromobenzene gave a low yield of 30% in **25** (Table 2, entry 2).

We also studied this reaction using 4-methylthiazole (Scheme 4). With this substrate, we could have observed the formation of the 2- or the 5-arylation products. In DMAc as the solvent using KOAc as the base, regioselective arylation on carbon C5 was observed.[5d] The use of pentan-1-ol as the solvent for such couplings preserves the regiochemical outcome of the arylation at the 5-position, and the products **30** and **31** were formed in quite good yields.

On the other hand, thiophenes or furans were found to give very low yields in coupling products when pentan-1-ol was employed as the solvent. For example, the coupling of 4-bromobenzonitrile with 2-propionylthiophene gave the desired product **32** in only 12% yield (Scheme 5). In DMAc, much better yields could be obtained.[8g]

The reactivity of 1,2-dimethylimidazole in pentan-1-ol was found to be quite similar to the reactivity of thiazoles. The reaction of 2-bromonaphthalene or 3-bromoquinoline gave **33** and **34** in good yields (Scheme 6).

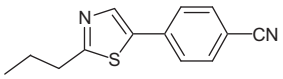
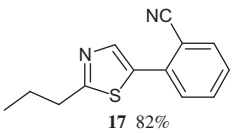
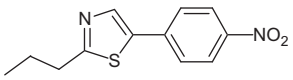
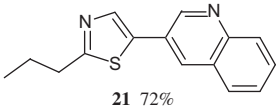
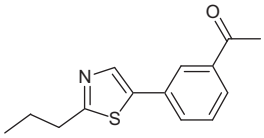
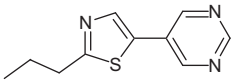
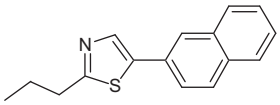
Finally, we examined if another amyl alcohol, 3-methylbutan-1-ol, could be employed for palladium-catalysed direct arylations (Table 3). As expected, the reaction of 2-*n*-propylthiazole with a set of aryl bromides in 3-methylbutan-1-ol also proceeds nicely, and gave similar yields than those obtained in pentan-1-ol.

In summary, we report here that a range of aryl bromides undergoe palladium-catalysed coupling via C–H bond activation/functionalisation reaction with thiazoles or 1,2-dimethylimidazole in moderate to good yields using pentan-1-ol or 3-methylbutan-1-ol as the solvents. These solvents, which are commercially available on a large scale at an affordable price, can be considered as green alternatives to DMF or DMAc, which are generally employed as the solvents for these transformations. For all these reactions, pentan-1-ol and 3-methylbutan-1-ol 99% were used without any purification. It should be noted that a wide variety of functional groups on the aryl bromide such as formyl, acetyl, propionyl, nitro, nitrile or fluoro are tolerated in these solvents.

Acknowledgements

We thank the Centre National de la Recherche Scientifique and 'Rennes Metropole' for providing financial support.

Table 3
Palladium-catalysed 5-arylation of 2-*n*-propylthiazole in 3-methylbutan-1-ol (Scheme 3)[19,20]

Entry	Product	Entry	Product
1	 **28** 0%	5	 **17** 82%
2	 **6****8** 1%	6	 **21** 72%
3	 **14** 76%	7	 **22** 13%
4	 **16** 74%		

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), aryl bromide (1 mmol), 2-*n*-propylthiazole (2 mmol), KOAc (2 mmol), 3-methylbutan-1-ol (5 mL), 20 h, 150 °C, isolated yields.

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19. *General procedure for coupling reactions*: In a typical experiment, the aryl bromide (1 mmol), heteroaromatic derivative (2 mmol), KOAc (0.196 g, 2 mmol) and $PdCl(C_3H_5)(dppb)$[17] (0.012 g, 0.02 mmol) were dissolved in pentan-1-ol or 3-methylbutanol (5 mL) (see tables) in a Schlenk tube under an argon atmosphere. The reaction mixture was stirred at 150 for 20 h. The solvent was removed in vacuo, then the crude mixture was purified by silica gel column chromatography.
20. *All compounds gave satisfactory ^1H, ^{13}C and elementary analysis*: ^1H NMR (200 MHz, $CDCl_3$) of new compounds: **13** δ 8.42 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 3.06 (t, J = 7.5 Hz, 2H), 1.83 (sext., J = 7.5 Hz, 2H), 1.10 (t, J = 7.5 Hz, 3H). **27** δ 7.70 (s, 1H), 7.68–7.45 (m, 3H), 3.06 (q, J = 7.5 Hz, 2H), 2.53 (s, 3H), 1.42 (t, J = 7.5 Hz, 3H). **31** δ 8.85 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.70–7.48 (m, 3H), 2.47 (s, 3H).