Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800596

Link to VoR: http://dx.doi.org/10.1002/adsc.201800596

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Exploring Green Solvents Associated to Pd/C as Heterogeneous Catalyst for Direct Arylation of Heteroaromatics with Aryl Bromides

Shuxin Mao,[a] Xinzhe Shi,[a] Jean-François Soulé*[a] and Henri Doucet*[a]

Abstract: Metal residues are certainly one of the major sources of contamination of products in metal-catalyzed direct arylation reactions. We found that the use of only 1 mol% of the heterogeneous catalyst Pd/C promotes very efficiently the direct arylations of most heteroaromatics. In the presence of this catalyst and potassium acetate as the base, the direct arylation of thiophenes, furans, pyrroles, thiazoles, imidazoles or isoxazoles, using aryl bromides as coupling partners, proceeds highly regioselectively and in moderate to very high yields. With several heteroarenes both electron-deficient and electron-rich aryl bromides were tolerated; moreover, with the most reactive heteroarenes, the Pd/C catalyst tolerated green solvents such as diethyl carbonate, 3-methylbutan-1-ol and pentan-1-ol, affording a synthetic scheme with low environmental impact.

Introduction

The access to arylated heteroaromatics is a very important research field in organic synthesis due to the physical or biological properties of such derivatives. For example, Dantrolene, Canagliflozin, Zolpidem, Atorvastatin, and Valdecoxib are currently employed for the treatment of various diseases (Figure 1).

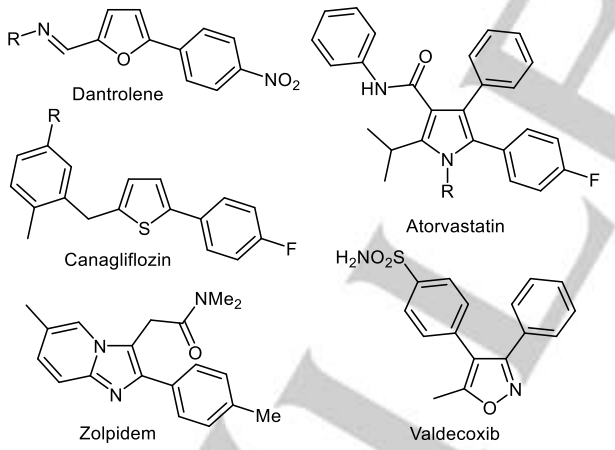

Figure 1. Examples of pharmaceuticals containing an arylated heteroaromatic

In 1990, Ohta et al. discovered that the arylation of several heteroaromatics using aryl halides as aryl source proceed *via* the C-H bond activation of heteroaromatics using $Pd(PPh_3)_4$ catalyst.[1] Since these seminal results, the so-called Pd-catalyzed "direct arylation" of heteroarenes was demonstrated to be an extremely powerful method for the preparation of a wide variety of arylated heterocycles.[2,3] This methodology is environmentally attractive, as the major reaction by-product is HX associated to a base, instead of the metallic salts mixture which is produced under the more classical Suzuki, Negishi or Stille cross-coupling reactions.[4] However, in most cases, direct arylations are currently performed using homogeneous palladium-catalysts, producing metal and ligands residues, which are a major issue in the pharmaceutical chemistry and also for some materials possessing specific optical properties. Moreover, these homogeneous catalysts are generally associated with relatively toxic solvents such as DMA, DMF, NMP, or dioxane.[5-10]

In recent years, a few solvents which can be considered as "green"[11] according to P. Anastas principles, have been employed for Pd-catalysed direct arylations of heteroaromatics.[12-17] For example, water was employed by Greaney and Djakovitch for the arylation of some 5-membered ring heterocycles;[13] whereas, Ackermann employed a polyethylene glycol solvent for the direct arylation of triazoles.[14] Carbonates, ethers or alcohols have been used as the solvents for the arylation of heteroarenes.[15-17] All these reactions were performed using homogeneous Pd-catalysts.

A few examples of Pd-catalyzed direct arylations of heteroarenes using heterogeneous palladium catalysts have been described.[18-24] The first one was reported in 1982 and employed Pd/C catalyst, but it was limited to isoxazoles as heteroarene and HMPT, which is considered as a toxic solvent, was used.[20] In 2013, Glorius et al. reported the heterogeneously catalyzed direct β-arylation of benzothiophenes with aryl chlorides using Pd/C catalyst in the presence of 10 mol% $CuCl_2$.[21] One year later, this group extended the use of Pd/C catalyst to the C4-arylation of thiophenes using aryl iodonium salts as aryl source and ethanol or water/ethanol mixtures as green solvents.[22] Only 1,2,3-triazole has been successfully employed in Pd-catalyzed direct arylation with aryl halides as aryl source using a heterogeneous catalyst in a green solvent.[18] For this reaction, Ackermann, Vaccaro et al. employed γ-valerolactone as renewable solvent associated with 5 mol% Pd/C. To our knowledge, the reactivity of other heteroaromatics and the influence of other "green" solvents using Pd/C catalyst for direct arylations with aryl halides as aryl source has not been described.

The use of the heterogeneous catalyst Pd/C presents several advantages: 1) it is not air or moisture sensitive and therefore easy to handle, 2) it can be easily removed from the product by simple filtration at the end of the reaction, 3) the product is contaminated with very low amount of Pd residues, 4) there is no phosphine residues, 5) it is easily available at an affordable

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cost, and 6) recycling of the recovered Pd/C is generally possible.

Herein, we report on the use of Pd/C for the direct arylations of a wide range of heteroaromatic derivatives with aryl bromides using, in several cases, solvents which can be considered as "green" and which are available on large scale at an affordable cost (Figure 2):

1) diethyl carbonate (DEC) which displays several advantages such as a high biodegradability, low acute toxicity and a low environmental impact in the course of its synthesis as it can be prepared from CO_2 and bioethanol;[25]

2) cyclopentyl methyl ether (CPME) which also presents several advantageous features such as limited miscibility in water which allows easy separation, low formation of peroxides (compared with THF or diisopropyl ether). Moreover, CPME can be manufactured by the addition of MeOH to cyclopentene which produces no apparent waste;[26]

3) 3-methylbutan-1-ol and pentan-1-ol which are biodegradable, are not considered as hazardous air pollutant solvents, are unlikely to have any adverse health effects, as they are found in several alcoholic beverages, and can be prepared by fermentation or by the reduction of 1-valeraldehyde or 3-methylbutyraldehyde with hydrogen.

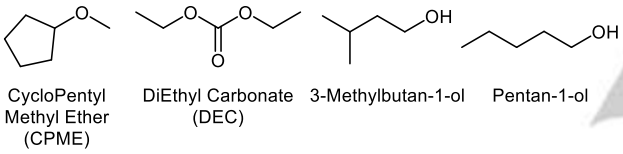
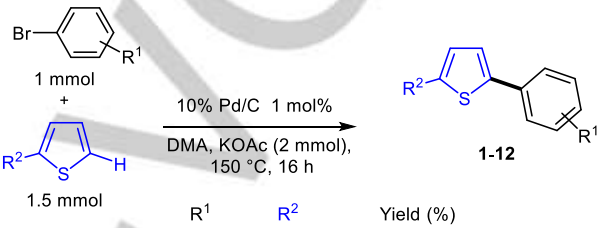


Figure 2. Green solvents employed for Pd/C catalyzed arylations

Results and Discussion

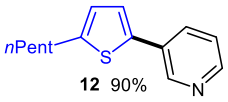
The first set of reactions using 2-*n*-pentylthiophene and 4-bromobenzonitrile as coupling partners was carried out under previously reported reaction conditions, but using 1 mol% of 10% Pd/C as the catalyst (Scheme 1).[5a] In the presence of the polar solvent *N*,*N*-dimethylacetamide (DMA), a high yield in the desired C5-arylated thiazole **1** was obtained. No formation of other arylated or diarylated thiophenes was detected by GC/MS analysis. As DMA is not a desirable solvent in terms of "green chemistry", the outcome of this reaction using four "greener" solvents was studied. The reaction in DEC or CPME with 1 mol% of 10% Pd/C catalyst afforded **1** in only 21% and <5% yields, respectively, due to partial conversions of 4-bromobenzonitrile. Conversely, 3-methylbutan-1-ol and pentan-1-ol afforded **1** in high yields with complete conversions of the aryl bromide.

Then, a set of aryl bromides was reacted with 2-*n*-pentylthiophene using 1 mol% of 10% Pd/C catalyst. High yields were generally obtained for the coupling of 2-*n*-pentylthiophene with aryl bromides in DMA. Both electron-withdrawing and electron-donating substituents were tolerated. It should be mentioned that for the reaction with 4-bromonitrobenzene, a higher yield in **4** was obtained using 3-methylbutan-1-ol instead of DMA as the solvent, due to the formation of a lower amount of side-products. A high yield in **7** was also obtained for the reaction of 2-bromobenzonitrile in 3-methylbutan-1-ol. Thiophene 2-carbonitrile also reacted nicely with 4-bromobenzonitrile and 4-bromoacetophenone using 1 mol% of 10% Pd/C catalyst in DMA affording **8** and **9** in 87% and 90% yields, respectively. Then, thiophenes substituted by ester or acetyl functions at C2 position were employed. In both cases, high yields in the expected coupling products **10** and **11** were obtained. 2-*n*-Pentylthiophene also underwent C5-arylation with 3-bromopyridine to give product **12** in 90% yield. The use of *p*-tolylboronic acid as aryl source instead of 4-bromobenzene for the preparation of **5**, under the same conditions, but using $Cu(OAc)_2$ as oxidant gave no coupling product.



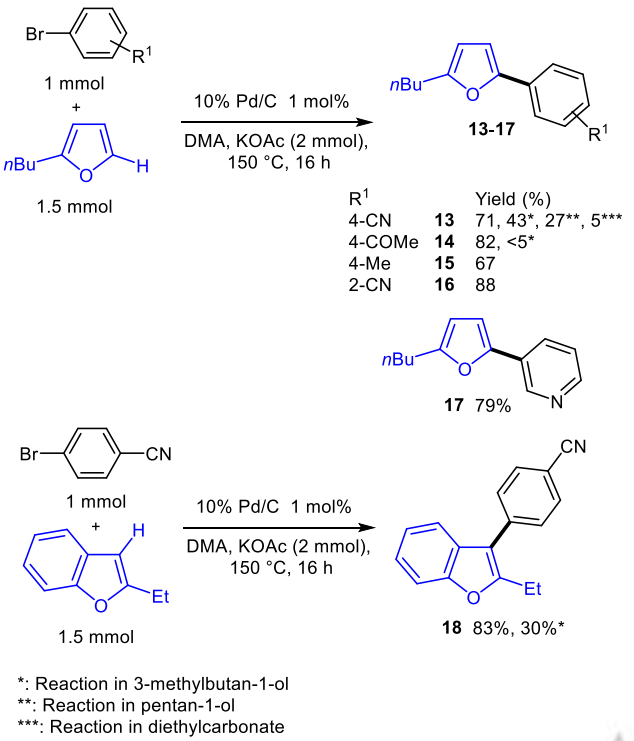
R^1	R^2		Yield (%)
4-CN	*n*Pent	**1**	91, 84*, 81**, 21***, <5****
4-COMe	*n*Pent	**2**	91
4-CO_2Et	*n*Pent	**3**	88, 54*
4-NO_2	*n*Pent	**4**	26, 67*
4-Me	*n*Pent	**5**	90, 0*****
4-MeO	*n*Pent	**6**	76
2-CN	*n*Pent	**7**	93*
4-CN	CN	**8**	87, 41*, 21***
4-COMe	CN	**9**	90
4-CN	COMe	**10**	79
4-CN	CO_2Et	**11**	84

*: Reaction in 3-methylbutan-1-ol
**: Reaction in pentan-1-ol
***: Reaction in diethylcarbonate
****: Reaction in cyclopentyl methyl ether
*****: *p*-tolylboronic acid instead of ArBr with 2 mmol of $Cu(OAc)_2$



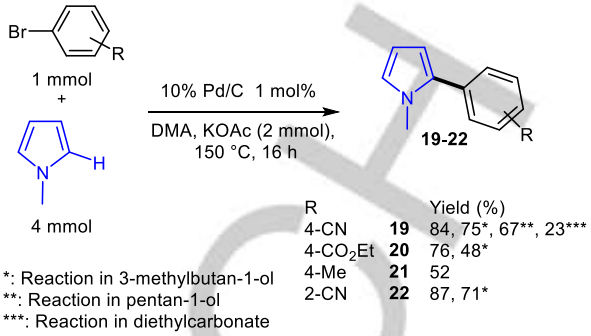
Scheme 1. Pd/C catalyzed coupling of thiophene derivatives with aryl bromides.

The reactivity of several furan derivatives in the presence of 1 mol% Pd/C catalyst was also examined (Scheme 2). The arylation of furan derivatives had been previously reported to proceed nicely in DMA using $PdCl(C_3H_5)$(dppb) as the catalyst.[6d] A poor reactivity of 2-*n*-butylfuran with 4-bromobenzonitrile was observed in DEC; whereas the reactions performed in 3-methylbutan-1-ol or DMA gave the desired product **13** in 43% and 71% yields, respectively. The arylation of 2-*n*-butylfuran in DMA using 1 mol% of 10% Pd/C catalyst also tolerated 4-acetyl- 4-methyl- or 2-cyano-substituents on the aryl bromide affording **14**-**16** in 67-88% yields. A good yield in product **17** was also obtained for the reaction with 3-bromopyridine. Under the same conditions, the reaction of 2-ethylbenzofuran with 4-bromobenzonitrile gave **18** in 83% yield.



Scheme 2. Pd/C catalyzed coupling of (benzo)furan derivatives with aryl bromides.

The use of 1 mol% of 10% Pd/C catalyst for the C2-arylation of 1-methylpyrrole was also successful; however, for these reactions, a larger excess of the heteroarene (4 equiv.) was employed in order to avoid the formation of 2,5-diarylated pyrroles as side-products (Scheme 3). With 2- and 4-bromobenzonitriles, good yields in the desired coupling products **19** and **22** were obtained in DMA and in 3-methylbutan-1-ol. Conversely, a moderate yield of **20** was obtained for the reaction of 1-methylpyrrole with ethyl 4-bromobenzoate in 3-methylbutan-1-ol, due to the formation of degradation products. With this aryl bromide, the use of DMA as the solvent allowed to obtain **20** in a higher yield. The reaction of 1-methylpyrrole with 4-bromotoluene gave the target product **21** in only 52% yield, as large amount of 4,4'-dimethyl-1,1'-biphenyl arising from the homo-coupling of 4-bromotoluene was also produced.

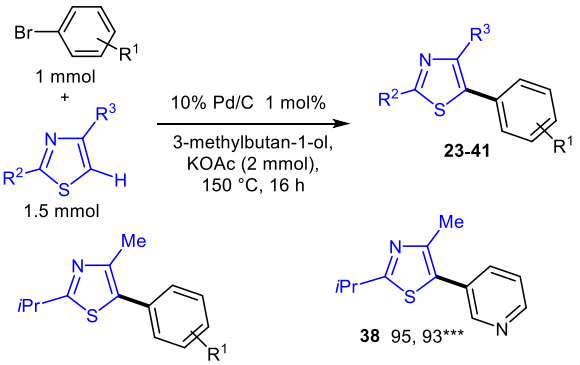


Scheme 3. Pd/C catalyzed coupling of pyrrole derivatives with aryl bromides.

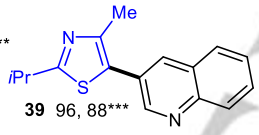
Then, we examined the reactivity of thiazoles with a set of aryl bromides in the presence of 1 mol% of 10% Pd/C. Firstly, various solvents were investigated for the arylation of 2-isopropyl-4-methylthiazole with 4-bromobenzonitrile using Pd/C as heterogeneous catalyst (Scheme 4). In the presence of the polar solvent DMA, a very high yield into the desired C5-arylated thiazole **23** was obtained. Then, the outcome of this reaction using four "greener" solvents was studied. The reaction using, CPME and 1 mol% of 10% Pd/C catalyst afforded **23** in only 48% yield due to a partial conversion of 4-bromobenzonitrile. Conversely, DEC, 3-methylbutan-1-ol and pentan-1-ol gave **23** in very high yields (94-97%) with complete conversions of the aryl bromide. The yield in **23** was very similar for a reaction performed on a larger scale (5 mmol of 2-isopropy-4-methylthiazole instead of 1 mmol) in 10 mL of 3-methylbutan-1-ol.

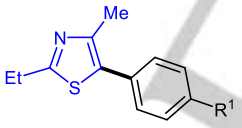
The reaction of several other *para*-substituted electron-deficient aryl bromides such as 4-bromobenzaldehyde, 4-bromoacetophenone, ethyl 4-bromobenzoate or 4-bromonitrobenzene with 2-isopropy-4-methylthiazole in 3-methylbutan-1-ol using 1 mol% of 10% Pd/C also gave the desired products **24**-**27** in very high yields. 4-Fluorobromobenzene afforded the coupling product **28** in a higher yield in DEC (97%) than in 3-methylbutan-1-ol (85%). The presence of the electron-donating *para*-substituents, methyl, *t*-butyl and methoxy on the aryl bromide was also tolerated providing **29**-**31** in 72-92% yields. The reaction of 2-isopropy-4-methylthiazole with 4-bromo-*N*,*N*-dimethylaniline in 3-methylbutan-1-ol gave **32** in only 41% yields due to partial conversion of the aniline derivative; however, the use of DMA as the solvent allowed to increase the yield to 78%. As expected, the reactivity of the *meta*-substituted 3,5-bis(trifluoromethyl)bromobenzene was found to be similar to *para*-substituted aryl bromides. The reactivity of four *ortho*-substituted aryl bromides was also examined. Due to their coordination and/or steric properties, *ortho*-substituents on aryl halides may have an important influence on the yields of Pd-catalysed reactions. 2-Cyano-, 2-trifluoromethyl- and 2-fluoro-substituents were tolerated, affording **34**, **36** and **37** in 85-94% yields, when the reactions were performed in 3-methylbutan-1-ol

or in DEC. The reaction with 2-bromonitrobenzene gave **35** in lower yields due to the formation of several unidentified degradation products. This novel environmentally friendly protocol using DEC or 3-methylbutan-1-ol and 1 mol% of 10% Pd/C was also effective for the direct couplings of 2-isopropyl-4-methylthiazole with 3-bromopyridine or 3-bromoquinoline. With these substrates, the target products **38** and **39** were obtained in 88-96% yields. 2-Ethyl-4-methylthiazole which is slightly less hindered than 2-isopropyl-4-methylthiazole exhibits a similar reactivity. Its reaction with 4-bromobenzonitrile and 4-bromopropiophenone in 3-methylbutan-1-ol or DEC using 1 mol% Pd/C gave **40** and **41** in 95-96% yields.



R^1		Yield (%)
4-CN	**23**	97, 96*, 97**, 94***, 48****, <5*****, 96******
4-CHO	**24**	89, 94***
4-COMe	**25**	97, <5*****
4-CO_2Et	**26**	95, 64***
4-NO_2	**27**	96, 96***, <5*****
4-F	**28**	85, 97***
4-Me	**29**	92, 58***
4-*t*Bu	**30**	89
4-MeO	**31**	72, 54***
4-NMe_2	**32**	41, 37**, 78****
3,5-CF_3	**33**	95, 96***
2-CN	**34**	94, 78***
2-NO_2	**35**	66, 35***
2-CF_3	**36**	85, 87***
2-F	**37**	93, 90***



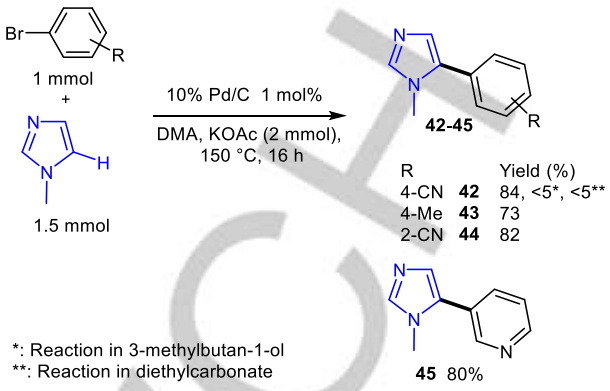


R^1		Yield (%)
CN	**40**	96, 96***
COEt	**41**	96, 95***

*: Reaction in DMA
**: Reaction in pentan-1-ol
***: Reaction in diethylcarbonate
****: Reaction in cyclopentyl methyl ether
*****: Using aryl chloride instead of aryl bromide
******: Thiazole 5 mmol, ArBr 7.5 mmol, KOAc 10 mmol, solvent 10 mL

Scheme 4. Pd/C catalyzed coupling of thiazole derivatives with aryl bromides.

We also studied the direct arylation of 1-methylimidazole using 1 mol% of 10% Pd/C catalyst (Scheme 5). In the course of this reaction, both positions C2 and C5 of imidazole might have been arylated. Using our procedure, in the presence of 2- or 4-bromobenzonitrile in DMA, a regioselective C5-arylation was observed, affording 42 and 44 in high yields. Moreover, good yields of target compounds 43 and 45 were obtained using the deactivated aryl bromide 4-bromotoluene, or a heteroarene.

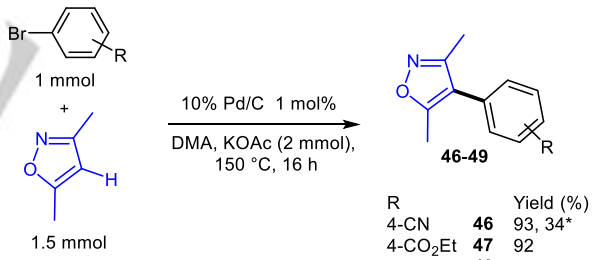


R		Yield (%)
4-CN	**42**	84, <5*, <5**
4-Me	**43**	73
2-CN	**44**	82

*: Reaction in 3-methylbutan-1-ol
**: Reaction in diethylcarbonate

Scheme 5. Pd/C catalyzed coupling of 1-methylimidazole with aryl bromides.

4-Arylisoxazoles are important structures due to their specific biological properties. For example, Valdecoxib (Figure 1) and Parecoxib, which contain this unit, are nonsteroidal anti-inflammatory drugs. The reaction of 3,5-dimethylisoxazole with 4-bromobenzonitrile in the presence of 1 mol% of 10% Pd/C catalyst in DMA gave the C4-arylated isoxazole in 93% yield (Scheme 6). Similar yields were obtained for the coupling of 3,5-dimethylisoxazole with ethyl 4-bromobenzoate and 2-bromobenzonitrile; whereas a lower yield in **48** was obtained with electron-rich 4-bromoanisole. The use of 3-methylbutan-1-ol as solvent for the arylation of 3,5-dimethylisoxazole was ineffective.



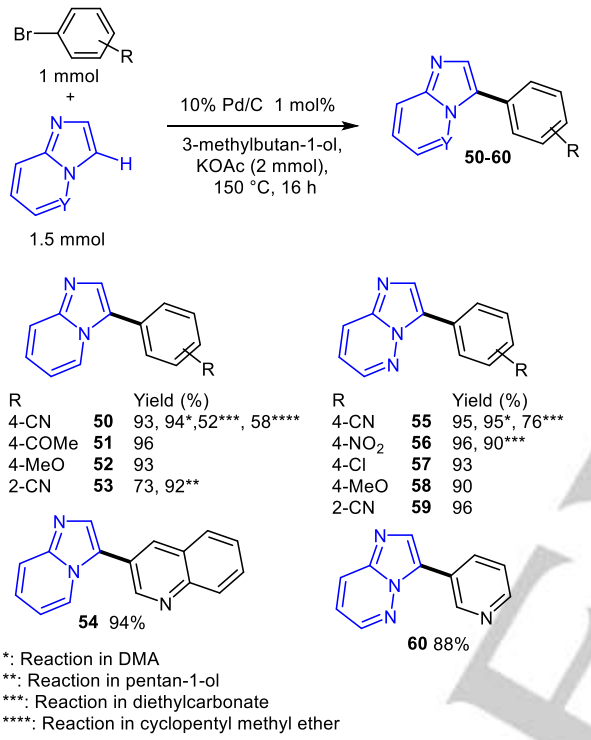
R		Yield (%)
4-CN	**46**	93, 34*
4-CO_2Et	**47**	92
4-MeO	**48**	75
2-CN	**49**	91, 10*

*: Reaction in 3-methylbutan-1-ol

Scheme 6. Pd/C catalyzed coupling of 3,5-dimethylisoxazole with aryl bromides.

Among heterocycles, imidazo[1,2-*a*]pyridines and imidazo[1,2-*b*]pyridazines display very important biological properties. For example, Zolpidem (Figure 1) is actually employed for the short-term treatment of insomnia, Miroprofen is a nonsteroidal anti-inflammatory drug and Ponatinib which contains an imidazo[1,2-*b*]pyridazine unit is used for the treatment of leukemia. Therefore, the discovery of effective procedures for the direct coupling of these two heteroarenes with aryl bromides is important for biochemists. We first studied the reactivity of imidazo[1,2-*a*]pyridine with *para*-substituted aryl bromides, using 1 mol% of 10% Pd/C catalyst in 3-methylbutan-1-ol. In all cases, very high yields of the expected coupling products **50**-**52** were

obtained. A lower yield in **53** was obtained for the reaction with 2-bromobenzonitrile in 3-methylbutan-1-ol, but the use of DMA as solvent afforded **53** in 92% yield. 3-Bromoquinoline was found to be very reactive in 3-methylbutan-1-ol, as **54** was obtained in 94% yield. The reactivity of imidazo[1,2-*b*]pyridazine is quite similar, as in all cases including with 2-bromobenzonitrile and 4-bromoanisole, the desired products **55**-**60** were obtained in good yields using 3-methylbutan-1-ol as the solvent. Moreover, high yields in **55** and **56** were also obtained in DEC.



Scheme 7. Pd/C catalyzed coupling of imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*]pyridazine with aryl bromides.

The mechanism of such direct arylations using Pd/C catalyst was not elucidated.[27] In 2003, Conlon et al. reported that the Suzuki-Miyaura reaction using heterogeneous Pd/C catalyst has a homogeneous component due to the formation of soluble Pd-species during the reaction.[27a] They assumed that the desorption of palladium from Pd/C occurs after oxidative addition of the aryl halide on the Pd/C surface, which generates a soluble Pd(II) species. As the direct arylations reported here employ quite similar reaction conditions, a homogeneous component in the catalytic cycle is also possible.

Conclusions

In summary, we demonstrated that Pd/C is an efficient catalyst for the direct arylation of a wide range of heteroaromatics. In the presence 1 mol% of 10% Pd/C, the direct arylation of thiazoles, thiophenes, furans, pyrroles, imidazoles or isoxazoles using aryl bromides as coupling partners proceeds highly regioselectively, and in moderate to very high yields. It should be mentioned that with several heteroarenes, both electron-deficient and electron-rich aryl bromides were reactive under these conditions, and a wide range of functionalities such as acetyl, propionyl, formyl, ester, nitro, nitrile, trifluoromethyl, chloro, fluoro, methoxy or amino on the aryl bromide is tolerated. Moreover, with the most reactive heteroarenes, this arylation could be performed in the "green" and renewable solvents 3-methylbutan-1-ol, pentan-1-ol or DEC. The use of a phosphine-free heterogeneous catalyst for such reactions reduces wastes and simplify purification procedure, and as the major by-products of these couplings are KBr/AcOH, this process is environmentally and economically attractive.

Experimental Section

Typical experiment for coupling reactions: The reaction of the aryl bromide (1 mmol), heteroaromatic (1.5 mmol) and KOAc (0.196, 2 mmol) in the presence of 10% Pd/C (0.011 g, 1 mol%) in the appropriate solvent (5 mL) (see schemes) under argon at 150 °C during 16 h, affords the corresponding product after cooling, evaporation of the solvent and filtration on silica gel (pentane/ether).

4-(5-Pentylthiophen-2-yl)benzonitrile (1)[28] 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-pentylthiophene (0.231 g, 1.5 mmol) affords **1** in 91% (0.232 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.57 (m, 4H), 7.23 (d, *J* = 3.6 Hz, 1H), 6.78 (d, *J* = 3.6 Hz, 1H), 2.83 (t, *J* = 7.5 Hz, 2H), 1.78-1.66 (m, 2H), 1.42-1.34 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 139.2, 138.9, 132.6, 125.6, 125.4, 124.8, 118.9, 109.8, 31.2, 30.2, 22.3, 13.9.

1-(4-(5-Pentylthiophen-2-yl)phenyl)ethan-1-one (2) 4-Bromoacetophenone (0.199 g, 1 mmol) and 2-pentylthiophene (0.231 g, 1.5 mmol) affords **2** in 91% (0.247 g) yield as a yellow solid: mp 94-96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 3.6 Hz, 1H), 6.78 (d, *J* = 3.6 Hz, 1H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.59 (s, 3H), 1.78-1.66 (m, 2H), 1.41-1.33 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 147.7, 140.0, 139.1, 135.2, 129.0, 125.4, 125.0, 124.3, 31.2, 30.2, 26.4, 22.3, 13.9. elemental analysis: calcd (%) for $C_{17}H_{20}OS$ (272.41): C 74.96, H 7.40; found: C 74.90, H 7.60.

Ethyl 4-(5-pentylthiophen-2-yl)benzoate (3) Ethyl 4-bromobenzoate (0.229 g, 1 mmol) and 2-pentylthiophene (0.231 g, 1.5 mmol) affords **3** in 88% (0.266 g) yield as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 3.6 Hz, 1H), 6.76 (d, *J* = 3.6 Hz, 1H), 4.38 (q, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 1.78-1.66 (m, 2H), 1.47-1.34 (m, 7H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 147.3, 140.2, 138.8, 130.0, 128.4, 125.2, 124.7, 124.1, 60.7, 31.1, 30.1, 22.3, 14.2, 13.9. elemental analysis: calcd (%) for $C_{18}H_{22}O_2S$ (302.43): C 71.49, H 7.33; found: C 71.40, H 6.98.

2-(4-Nitrophenyl)-5-pentylthiophene (4) 4-Bromonitrobenzene (0.202 g, 1 mmol) and 2-pentylthiophene (0.231 g, 1.5 mmol) affords **4** in 67% (0.184 g) yield as a yellow solid: mp 60-62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 3.6 Hz, 1H), 6.81 (d, *J* = 3.6 Hz, 1H), 2.84 (t, *J* = 7.5 Hz, 2H), 1.77-1.66 (m, 2H), 1.44-1.32 (m, 4H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 149.3, 146.2, 141.0, 138.8, 125.9, 125.6, 125.4, 124.4, 31.2, 30.3, 22.4, 14.0. elemental analysis: calcd (%) for $C_{15}H_{17}NO_2S$ (275.37): C 65.43, H 6.22; found: C 65.34, H 6.12.

2-Pentyl-5-(*p*-tolyl)thiophene (5) 4-Bromotoluene (0.171 g, 1 mmol) and 2-pentylthiophene (0.231 g, 1.5 mmol) affords **5** in 90% (0.220 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 3.6 Hz, 1H), 6.73 (d, *J* = 3.6 Hz, 1H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.36 (s, 3H), 1.78-1.65 (m, 2H), 1.43-1.33 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 141.7, 136.7, 132.0, 129.4, 125.4, 124.8, 122.1, 31.4, 31.3, 30.2, 22.4, 21.1, 14.0. elemental analysis: calcd (%) for $C_{16}H_{20}S$ (244.40): C 78.63, H 8.25; found: C 78.90, H 8.02.

2-(4-Methoxyphenyl)-5-pentylthiophene (6)[29] 4-Bromoanisole (0.187 g, 1 mmol) and 2-pentylthiophene (0.231 g, 1.5 mmol) affords **6** in 76% (0.198 g) yield as a white solid: mp 62-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 3.6 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 3.6 Hz, 1H), 3.83 (s, 3H), 2.82 (t, *J* = 7.5 Hz, 2H), 1.77-1.66 (m, 2H), 1.44-1.32 (m, 4H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 145.4, 142.2, 128.4, 127.4, 125.5, 122.3, 114.9, 56.0, 32.0, 30.9, 23.1, 14.7.

2-(5-Pentylthiophen-2-yl)benzonitrile (7) 2-Bromobenzonitrile (0.182 g, 1 mmol) and 2-pentylthiophene (0.231 g, 1.5 mmol) affords **7** in 93% (0.237 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.65-7.53 (m, 2H), 7.51 (d, *J* = 3.6 Hz, 1H), 7.33 (td, *J* = 8.0, 1.7 Hz, 1H), 6.85 (d, *J* = 3.6 Hz, 1H), 2.86 (t, *J* = 7.5 Hz, 2H), 1.79-1.67 (m, 2H), 1.47-1.34 (m, 4H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 137.7, 136.5, 134.2, 132.7, 129.1, 127.3, 126.8, 125.2, 119.0, 109.2, 31.2, 31.1, 30.0, 22.3, 13.9. elemental analysis: calcd (%) for $C_{16}H_{17}NS$ (255.38): C 75.25, H 6.71; found: C 75.08, H 6.98.

5-(4-Cyanophenyl)thiophene-2-carbonitrile (8)[17] 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-thiophenecarbonitrile (0.164 g, 1.5 mmol) affords **8** in 87% (0.183 g) yield as a yellow solid: mp 212-214 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 3.9 Hz, 1H), 7.39 (d, *J* = 3.9 Hz, 1H).

5-(4-Acetylphenyl)thiophene-2-carbonitrile (9)[17] 4-Bromoacetophenone (0.199 g, 1 mmol) and 2-thiophenecarbonitrile (0.164 g, 1.5 mmol) affords **9** in 90% (0.204 g) yield as a yellow solid: mp 162-164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.5 Hz, 2H), 7.69 7.93 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 3.9 Hz, 1H), 7.39 (d, *J* = 3.9 Hz, 1H), 2.62 (s, 3H).

4-(5-Acetylthiophen-2-yl)benzonitrile (10)[17] 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-acetylthiophene (0.189 g, 1.5 mmol) affords **10** in 79% (0.179 g) yield as a yellow solid: mp 166-168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.5 Hz, 2H), 7.70-7.65 (m, 3H), 7.40 (d, *J* = 3.9 Hz, 1H), 2.57 (s, 3H).

Ethyl 5-(4-cyanophenyl)thiophene-2-carboxylate (11)[8d] 4-Bromobenzonitrile (0.182 g, 1 mmol) and ethyl thiophene-2-carboxylate (0.234 g, 1.5 mmol) affords **11** in 84% (0.216 g) yield as a yellow solid: mp 134-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 3.9 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 3.9 Hz, 1H), 4.37 (q, *J* = 7.6 Hz, 2H), 1.39 (t, *J* = 7.6 Hz, 3H).

3-(5-Pentylthiophen-2-yl)pyridine (12) 3-Brompyridine (0.158 g, 1 mmol) and 2-pentylthiophene (0.231 g, 1.5 mmol) affords **12** in 90% (0.208 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, *J* = 2.0 Hz, 1H), 8.44 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.77 (ddd, *J* = 8.0, 2.2, 1.7 Hz, 1H), 7.22 (ddd, *J* = 8.0, 4.8, 0.6 Hz, 1H), 7.14 (d, *J* = 3.6 Hz, 1H), 6.75 (d, *J* = 3.6 Hz, 1H), 2.80 (t, *J* = 7.5 Hz, 2H), 1.75-1.63 (m, 2H), 1.40-1.28 (m, 4H), 0.90 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.1, 146.6, 137.6, 132.4, 130.7, 125.3, 123.9, 123.5, 31.3, 31.2, 30.2, 22.4, 14.0. elemental analysis: calcd (%) for $C_{14}H_{17}NS$ (231.36): C 72.68, H 7.41; found: C 72.78, H 7.57.

4-(5-Butylfuran-2-yl)benzonitrile (13)[6c] 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-butylfuran (0.186 g, 1.5 mmol) affords **13** in 71% (0.160 g) yield as a yellow solid: mp 58-60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 3.3 Hz, 1H), 6.11 (d, *J* = 3.3 Hz, 1H), 2.70 (t, *J* = 7.5 Hz, 2H), 1.67 (quint., *J* = 7.5 Hz, 2H), 1.43 (sext., *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 150.1, 134.9, 132.5, 123.3, 119.1, 109.4, 109.1, 107.6, 30.0, 27.9, 22.2, 13.4.

1-(4-(5-Butylfuran-2-yl)phenyl)ethan-1-one (14)[15a] 4-Bromoacetophenone (0.199 g, 1 mmol) and 2-butylfuran (0.186 g, 1.5 mmol) affords **14** in 82% (0.198 g) yield as a white solid: mp 43-45 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 3.3 Hz, 1H), 6.10 (d, *J* = 3.3 Hz, 1H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.59 (s, 3H), 1.67 (quint., *J* = 7.5 Hz, 2H), 1.43 (sext., *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 158.0, 150.9, 135.2, 134.9, 128.9, 122.9, 108.4, 107.4, 30.1, 27.9, 26.4, 22.2.

2-Butyl-5-(*p*-tolyl)furan (15)[6a] 4-Bromotoluene (0.171 g, 1 mmol) and 2-butylfuran (0.186 g, 1.5 mmol) affords **15** in 67% (0.143 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.48 (d, *J* = 3.3 Hz, 1H), 6.04 (d, *J* = 3.3 Hz, 1H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.36 (s, 3H), 1.67 (quint., *J* = 7.5 Hz, 2H), 1.43 (sext., *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H).

2-(5-Butylfuran-2-yl)benzonitrile (16)[6c] 2-Bromobenzonitrile (0.182 g, 1 mmol) and 2-butylfuran (0.186 g, 1.5 mmol) affords **16** in 88% (0.198 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.55 (td, *J* = 7.8, 1.3 Hz, 1H), 7.24 (td, *J* = 7.8, 1.1 Hz, 1H), 7.20 (d, *J* = 3.3 Hz, 1H), 6.15 (d, *J* = 3.3 Hz, 1H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.67 (quint., *J* = 7.5 Hz, 2H), 1.43 (sext., *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 147.9, 134.0, 133.4, 132.7, 126.3, 125.3, 119.1, 111.3, 107.6, 106.0, 29.9, 27.7, 22.2, 13.7.

3-(5-Butylfuran-2-yl)pyridine (17)[6c] 3-Bromopyridine (0.158 g, 1 mmol) and 2-butylfuran (0.186 g, 1.5 mmol) affords **17** in 79% (0.159 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.42 (d, *J* = 4.8 Hz, 1H), 7.86 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.24 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.61 (d, *J* = 3.3 Hz, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.67 (quint., *J* = 7.5 Hz, 2H), 1.40 (sext., *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H).

4-(2-Ethylbenzofuran-3-yl)benzonitrile (18)[6d] 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-ethylbenzofuran (0.219 g, 1.5 mmol) affords **18** in 83% (0.205 g) yield as a white solid: mp 114-116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 2.90 (q, *J* = 7.5 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 154.0, 138.0, 132.5, 129.4, 127.8, 124.1, 123.0, 119.0, 118.8, 114.9, 111.1, 110.5, 20.3, 12.8.

4-(1-Methylpyrrol-2-yl)benzonitrile (19)[7c] 4-Bromobenzonitrile (0.182 g, 1 mmol) and *N*-methylpyrrole (0.324 g, 4 mmol) affords **19** in 84% (0.153 g) yield as a white solid: mp 102-104 °C. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 6.82 (t, *J* = 2.2 Hz, 1H), 6.38 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.27 (dd, *J* = 3.6, 2.6 Hz, 1H), 3.75 (s, 3H).

Ethyl 4-(1-methylpyrrol-2-yl)benzoate (20)[30] Ethyl 4-bromobenzoate (0.229 g, 1 mmol) and *N*-methylpyrrole (0.324 g, 4 mmol) affords **20** in 76% (0.174 g) yield as a yellow solid: mp 61-63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 6.79 (t, *J* = 2.2 Hz, 1H), 6.38 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.26 (dd, *J* = 3.6, 2.6 Hz, 1H), 4.43 (q, *J* = 7.6 Hz, 2H), 3.74 (s, 3H), 1.45 (t, *J* = 7.6 Hz, 3H).

1-Methyl-2-(*p*-tolyl)pyrrole (21)[7c] 4-Bromotoluene (0.171 g, 1 mmol) and *N*-methylpyrrole (0.324 g, 4 mmol) affords **21** in 52% (0.089 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.70 (t, *J* = 2.2 Hz, 1H), 6.22-6.18 (m, 2H), 3.65 (s, 3H), 2.38 (s, 3H).

2-(1-Methylpyrrol-2-yl)benzonitrile (22)[7c] 2-Bromobenzonitrile (0.182 g, 1 mmol) and *N*-methylpyrrole (0.324 g, 4 mmol) affords **22** in 87% (0.158 g) yield as a white solid: mp 94-96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.61 (td, *J* = 7.8, 1.4 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.40 (td, *J* = 8.5, 1.2 Hz, 1H), 6.80 (t, *J* = 2.2 Hz, 1H), 6.42 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.26 (dd, *J* = 3.6, 2.6 Hz, 1H), 3.62 (s, 3H).

4-(2-Isopropyl-4-methylthiazol-5-yl)benzonitrile (23) 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **23** in 97% (0.234 g) yield as a white solid: mp 58-60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 3.30 (sept., *J* = 7.5 Hz, 1H), 2.50 (s, 3H), 1.42 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 148.5, 137.4, 132.3, 129.4, 128.6, 118.5, 110.8, 33.4, 23.1, 16.4. elemental analysis: calcd (%) for $C_{14}H_{14}N_2S$ (242.34): C 69.39, H 5.82; found: C 69.14, H 5.78.

4-(2-Isopropyl-4-methylthiazol-5-yl)benzaldehyde (24) 4-Bromobenzaldehyde (0.185 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **24** in 94% (0.230 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 3.25 (sept., *J* = 7.5 Hz, 1H), 2.48 (s, 3H), 1.38 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 176.5, 148.3, 138.8, 134.9, 129.9, 129.2, 129.1, 33.3, 23.0, 16.4. elemental analysis: calcd (%) for $C_{14}H_{15}NOS$ (245.34): C 68.54, H 6.16; found: C 68.30, H 6.01.

1-(4-(2-Isopropyl-4-methylthiazol-5-yl)phenyl)ethan-1-one (25) 4-Bromoacetophenone (0.199 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **25** in 97% (0.251 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 3.27 (sept., *J* = 7.5 Hz, 1H), 2.59 (s, 3H), 2.48 (s, 3H), 1.39 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 176.3, 148.0, 137.4, 135.7, 129.3, 128.9, 128.6, 33.3, 26.5, 23.1, 16.4. elemental analysis: calcd (%) for $C_{14}H_{17}NOS$ (259.37): C 69.46, H 6.61; found: C 69.38, H 6.40.

Ethyl 4-(2-isopropyl-4-methylthiazol-5-yl)benzoate (26) Ethyl 4-bromobenzoate (0.229 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **26** in 95% (0.274 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 4.37 (q, *J* = 7.5 Hz, 2H), 3.25 (sept., *J* = 7.5 Hz, 1H), 2.48 (s, 3H), 1.43-1.35 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 166.0, 147.8, 137.1, 129.7, 129.4, 129.1, 128.7, 60.9, 33.3, 23.0, 16.3, 14.2. elemental analysis: calcd (%) for $C_{16}H_{19}NO_2S$ (289.39): C 66.41, H 6.62; found: C 66.58, H 6.45.

2-Isopropyl-4-methyl-5-(4-nitrophenyl)thiazole (27) 4-Bromonitrobenzene (0.202 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **27** in 96% (0.251 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 3.28 (sept., *J* = 7.5 Hz, 1H), 2.51 (s, 3H), 1.42 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 148.9, 146.5, 139.4, 129.3, 128.2, 123.8, 33.3, 23.0, 16.5. elemental analysis: calcd (%) for $C_{13}H_{14}N_2O_2S$ (262.33): C 59.52, H 5.38; found: C 59.60, H 5.49.

5-(4-Fluorophenyl)-2-isopropyl-4-methylthiazole (28) 4-Fluorobromobenzene (0.175 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.211 g, 1.5 mmol) affords **28** in 97% (0.228 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.07 (t, *J* = 8.6 Hz, 2H), 3.27 (sept., *J* = 7.5 Hz, 1H), 2.42 (s, 3H), 1.40 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 162.1 (d, *J* = 247.8 Hz), 146.9, 130.8 (d, *J* = 8.1 Hz), 129.3, 128.5 (d, *J* = 3.5 Hz), 115.6 (d, *J* = 21.8 Hz), 33.3, 23.2, 15.9. elemental analysis: calcd (%) for $C_{13}H_{14}FNS$ (235.32): C 66.35, H 6.00; found: C 66.20, H 5.74.

2-Isopropyl-4-methyl-5-(*p*-tolyl)thiazole (29) 4-Bromotoluene (0.171 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.211 g, 1.5 mmol) affords **29** in 92% (0.212 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 3.27 (sept., *J* = 7.5 Hz, 1H), 2.46 (s, 3H), 2.38 (s, 3H), 1.41 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 146.4, 137.2, 130.4, 129.5, 129.2, 128.9, 33.3, 23.2, 21.1, 16.0. elemental analysis: calcd (%) for $C_{14}H_{17}NS$ (231.36): C 72.68, H 7.41; found: C 72.64, H 7.32.

5-(4-(*tert*-Butyl)phenyl)-2-isopropyl-4-methylthiazole (30) 4-*tert*-Butylbromobenzene (0.213 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.211 g, 1.5 mmol) affords **30** in 89% (0.243 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 3.28 (sept., *J* = 7.5 Hz, 1H), 2.47 (s, 3H), 1.41 (d, *J* = 7.5 Hz, 6H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 150.4, 146.5, 130.4, 129.6, 128.8, 125.5, 34.6, 33.3, 31.2, 23.2, 16.1. elemental analysis: calcd (%) for $C_{17}H_{23}NS$ (273.44): C 74.67, H 8.48; found: C 74.81, H 8.31.

2-Isopropyl-5-(4-methoxyphenyl)-4-methylthiazole (31) 4-Bromoanisole (0.187 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.211 g, 1.5 mmol) affords **31** in 72% (0.178 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 3.84 (s, 3H), 3.25 (sept., *J* = 7.5 Hz, 1H), 2.43 (s, 3H), 1.40 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 159.0, 146.2, 130.4, 130.2, 124.8, 114.0, 55.3, 33.3, 23.2, 16.0. elemental analysis: calcd (%) for $C_{14}H_{17}NOS$ (247.36): C 67.98, H 6.93; found: C 68.12, H 6.78.

4-(2-Isopropyl-4-methylthiazol-5-yl)-*N*,*N*-dimethylaniline (32) 4-Bromo-*N*,*N*-dimethylaniline (0.200 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.211 g, 1.5 mmol) affords **32** in 78% (0.203 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 2H), 3.27 (sept., *J* = 7.5 Hz, 1H), 2.99 (s, 6H), 2.45 (s, 3H), 1.40 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 149.8, 145.5, 131.1, 130.0, 120.2, 112.2, 40.4, 33.3, 23.3, 16.1. elemental analysis: calcd (%) for $C_{15}H_{20}N_2S$ (260.40): C 69.19, H 7.74; found: C 69.00, H 7.88.

5-(3,5-Bis(trifluoromethyl)phenyl)-2-isopropyl-4-methylthiazole (33) 3,5-Bis(trifluoromethyl)bromobenzene (0.293 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.211 g, 1.5 mmol) affords **33** in 96% (0.339 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 2H), 7.85 (s, 1H), 3.33 (sept., *J* = 7.5 Hz, 1H), 2.51 (s, 3H), 1.45 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 148.9, 135.0, 132.0 (q, *J* = 33.5 Hz), 129.0 (m), 127.3, 123.1 (q, *J* = 273.0 Hz), 121.0 (m), 33.5, 23.1, 16.1.

elemental analysis: calcd (%) for $C_{15}H_{13}F_6NS$ (353.33): C 50.99, H 3.71; found: C 51.20, H 3.64.

2-(2-Isopropyl-4-methylthiazol-5-yl)benzonitrile (34) 2-Bromobenzonitrile (0.182 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **34** in 94% (0.227 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.60 (td, *J* = 7.8, 1.4 Hz, 1H), 7.48-7.42 (m, 2H), 3.28 (sept., *J* = 7.5 Hz, 1H), 2.34 (s, 3H), 1.40 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 149.9, 136.1, 133.3, 132.5, 131.8, 128.3, 125.5, 117.7, 113.5, 33.3, 23.0, 16.0. elemental analysis: calcd (%) for $C_{14}H_{14}N_2S$ (242.34): C 69.39, H 5.82; found: C 69.50, H 5.98.

2-Isopropyl-4-methyl-5-(4-nitrophenyl)thiazole (35) 2-Bromonitrobenzene (0.202 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **35** in 66% (0.173 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 (td, *J* = 7.5, 1.3 Hz, 1H), 7.44 (dd, *J* = 8.0, 1.3 Hz, 1H), 3.29 (sept., *J* = 7.5 Hz, 1H), 2.21 (s, 3H), 1.41 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 150.0, 149.5, 133.6, 132.4, 129.3, 126.9, 124.4, 123.9, 33.3, 23.1, 15.5. elemental analysis: calcd (%) for $C_{13}H_{14}N_2O_2S$ (262.33): C 59.52, H 5.38; found: C 59.47, H 5.20.

2-Isopropyl-4-methyl-5-(2-(trifluoromethyl)phenyl)thiazole (36) 2-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **36** in 87% (0.248 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 746 (td, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 3.27 (sept., *J* = 7.5 Hz, 1H), 2.14 (s, 3H), 1.39 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 149.6, 133.7, 131.4, 131.1, 130.6 (q, *J* = 29.8 Hz), 128.7, 126.2 (q, *J* = 5.3 Hz), 125.4, 123.6 (q, *J* = 273.8 Hz), 33.2, 23.1, 15.5. elemental analysis: calcd (%) for $C_{14}H_{14}F_3NS$ (285.33): C 58.93, H 4.95; found: C 58.99, H 4.20.

5-(2-Fluorophenyl)-2-isopropyl-4-methylthiazole (37) 2-Fluorobromobenzene (0.175 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.211 g, 1.5 mmol) affords **37** in 93% (0.218 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.30 (m, 2H), 7.20-7.12 (m, 2H), 3.31 (sept., *J* = 7.5 Hz, 1H), 2.36 (s, 3H), 1.42 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 159.7 (d, *J* = 248.8 Hz), 149.2, 132.1 (d, *J* = 2.6 Hz), 129.8 (d, *J* = 8.1 Hz), 124.1 (d, *J* = 3.8 Hz), 123.0, 120.0 (d, *J* = 15.3 Hz), 116.0 (d, *J* = 22.2 Hz), 33.3, 23.2, 15.9 (d, *J* = 2.8 Hz). elemental analysis: calcd (%) for $C_{13}H_{14}FNS$ (235.32): C 66.35, H 6.00; found: C 66.54, H 5.78.

2-Isopropyl-4-methyl-5-(pyridin-3-yl)thiazole (38) 3-Bromopyridine (0.158 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.211 g, 1.5 mmol) affords **38** in 95% (0.207 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (bs, 1H), 8.55 (bs, 1H), 7.70 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.32 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.25 (sept., *J* = 7.5 Hz, 1H), 2.45 (s, 3H), 1.40 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 146.6, 148.4, 148.2, 136.1, 128.8, 126.5, 123.3, 33.4, 23.1, 16.0. elemental analysis: calcd (%) for $C_{12}H_{14}N_2S$ (218.32): C 66.02, H 6.46; found: C 65.87, H 6.34.

2-Isopropyl-4-methyl-5-(quinolin-3-yl)thiazole (39) 3-Bromoquinoline (0.208 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.211 g, 1.5 mmol) affords **39** in 96% (0.257 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (d, *J* = 1.9 Hz, 1H), 8.15 (d, *J* = 1.9 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.72 (t, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 3.30 (sept., *J* = 7.5 Hz, 1H), 2.54 (s, 3H), 1.44 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 150.6, 148.4, 147.0, 135.1, 129.6, 129.2, 127.7, 127.5, 127.2, 126.7, 125.9, 33.4, 23.1, 16.1. elemental analysis: calcd (%) for $C_{16}H_{16}N_2S$ (268.38): C 71.61, H 6.01; found: C 71.42, H 5.88.

4-(2-Ethyl-4-methylthiazol-5-yl)benzonitrile (40)[8a] 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.190 g, 1.5 mmol) affords **40** in 96% (0.219 g) yield as a white solid: mp 54-56 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 3.04 (q, *J* = 7.5 Hz, 2H), 2.51 (s, 3H), 1.43 (t, *J* = 7.5 Hz, 3H).

1-(4-(2-Ethyl-4-methylthiazol-5-yl)phenyl)propan-1-one (41) 4-Bromopropiophenone (0.213 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.190 g, 1.5 mmol) affords **41** in 96% (0.248 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 2.98 (q, *J* = 7.5 Hz, 4H), 2.47 (s, 3H), 1.38 (t, *J* = 7.5 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 171.1, 148.0, 137.0, 135.5, 129.8, 128.9, 128.3, 31.7, 26.9, 16.3, 14.2, 8.2. elemental analysis: calcd (%) for $C_{15}H_{17}NOS$ (259.37): C 69.46, H 6.61; found: C 69.60, H 6.51.

4-(1-Methylimidazol-5-yl)benzonitrile (42)[9e] 4-Bromobenzonitrile (0.182 g, 1 mmol) and 1-methylimidazole (0.123 g, 1.5 mmol) affords **42** in 84% (0.154 g) yield as a white solid: mp 146-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.56 (bs, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.20 (bs, 1H), 3.71 (s, 3H).

1-Methyl-5-(*p*-tolyl)imidazole (43)[9e] 4-Bromotoluene (0.171 g, 1 mmol) and 1-methylimidazole (0.123 g, 1.5 mmol) affords **43** in 73% (0.125 g) yield as a white solid: mp 40-42 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.53 (bs, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.09 (bs, 1H), 3.67 (s, 3H), 2.42 (s, 3H).

2-(1-Methylimidazol-5-yl)benzonitrile (44) 2-Bromobenzonitrile (0.182 g, 1 mmol) and 1-methylimidazole (0.123 g, 1.5 mmol) affords **44** in 82% (0.150 g) yield as a white solid: mp 156-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.61 (td, *J* = 7.8, 1.3 Hz, 1H), 7.52 (bs, 1H), 7.44 (td, *J* = 7.8, 1.1 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.16 (bs, 1H), 3.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 133.6, 133.2, 132.9, 131.0, 130.3, 129.3, 128.8, 117.9, 113.0, 32.3. elemental analysis: calcd (%) for $C_{11}H_9N_3$ (183.21): C 72.11, H 4.95; found: C 72.00, H 4.87.

3-(1-Methylimidazol-5-yl)pyridine (45)[9e] 3-Bromopyridine (0.158 g, 1 mmol) and 1-methylimidazole (0.123 g, 1.5 mmol) affords **45** in 80% (0.127 g) yield as a white solid: mp 124-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, *J* = 1.6 Hz, 1H), 8.63 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.72 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.59 (bs, 1H), 7.40 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.19 (bs, 1H), 3.71 (s, 3H).

4-(3,5-Dimethylisoxazol-4-yl)benzonitrile (46)[10] 4-Bromobenzonitrile (0.182 g, 1 mmol) and 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) affords **46** in 93% (0.184 g) yield as a white solid: mp 113-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 2.42 (s, 3H), 2.27 (s, 3H).

Ethyl 4-(3,5-dimethylisoxazol-4-yl)benzoate (47)[31] Ethyl 4-bromobenzoate (0.229 g, 1 mmol) and 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) affords **47** in 92% (0.225 g) yield as a white solid: mp 68-70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 4.38 (q, *J* = 7.6 Hz, 2H), 2.40 (s, 3H), 2.26 (s, 3H), 1.38 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 165.6, 158.2, 135.1, 129.9, 129.5, 128.8, 115.9, 61.0, 14.2, 11.5, 10.7.

4-(4-Methoxyphenyl)-3,5-dimethylisoxazole (48)[10] 4-Bromoanisole (0.187 g, 1 mmol) and 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) affords **48** in 75% (0.152 g) yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 3H), 2.38 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 159.0, 158.8, 130.3, 122.6, 116.2, 114.2, 55.3, 11.5, 10.8.

2-(3,5-Dimethylisoxazol-4-yl)benzonitrile (49)[10] 2-Bromobenzonitrile (0.182 g, 1 mmol) and 3,5-dimethylisoxazole (0.144 g, 1.5 mmol) affords **49** in 91% (0.180 g) yield as a white solid: mp 115-117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.66 (td, *J* = 7.9, 1.4 Hz, 1H), 7.49 (td, *J* = 8.5, 1.2 Hz, 1H),7.32 (d, *J* = 7.8 Hz, 1H), 2.35 (s, 3H), 2.19 (s, 3H).

4-(Imidazo[1,2-*a*]pyridin-3-yl)benzonitrile (50)[9f] 4-Bromobenzonitrile (0.182 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **50** in 94% (0.206 g) yield as a yellow solid: mp 175-177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 6.8 Hz, 1H), 7.84-7.72 (m, 4H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.29 (dd, *J* = 8.6, 6.8 Hz, 1H), 6.92 (t, *J* = 6.8 Hz, 1H).

1-(4-(Imidazo[1,2-*a*]pyridin-3-yl)phenyl)ethan-1-one (51)[9f] 4-Bromoacetophenone (0.199 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **51** in 96% (0.226 g) yield as a yellow solid: mp 160-162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 6.9 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 2H), 7.73 (s, 1H), 7.70-7.60 (m, 3H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.82 (t, *J* = 7.2 Hz, 1H). 2.59 (s, 3H).

3-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridine (52)[9f] 4-Bromoanisole (0.187 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **52** in 93% (0.208 g) yield as a white solid: mp 85-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 6.8 Hz, 1H), 7.68-7.60 (m, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.0Hz, 2H), 6.76 (t, *J* = 6.8 Hz, 1H), 3.85 (s, 3H).

2-(Imidazo[1,2-*a*]pyridin-3-yl)benzonitrile (53)[9f] 2-Bromobenzonitrile (0.182 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **53** in 92% (0.201 g) yield as a white solid: mp 148-150 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ 8.35 (d, *J* = 6.8 Hz, 1H), 7.99 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.92-7.80 (m, 3H), 7.71-7.62 (m, 2H), 7.36 (ddd, *J* = 8.6, 6.8, 1.1 Hz, 1H), 6.99 (td, *J* = 6.8, 0.9 Hz, 1H).

3-(Imidazo[1,2-a]pyridin-3-yl)quinoline (54)[9f] 3-Bromoquinoline (0.208 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **54** in 94% (0.230 g) yield as a yellow solid: mp 146-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (d, *J* = 2.1 Hz, 1H), 8.38 (dt, *J* = 7.0, 1.0 Hz, 1H), 8.32 (d, *J* = 2.1 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.86 (s, 1H), 7.80-7.70 (m, 2H), 7.61 (td, J = 7.0, 1.1, 1H), 7.27 (ddd, *J* = 8.6, 6.8, 1.1 Hz, 1H), 6.87 (td, *J* = 6.8, 0.9 Hz, 1H).

4-(Imidazo[1,2-*b*]pyridazin-3-yl)benzonitrile (55)[15b] 4-Bromobenzonitrile (0.182 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.178 g, 1.5 mmol) affords **55** in 95% (0.209 g) yield as a white solid: mp 159-161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 4.3 Hz, 1H), 8.22 (d, *J* = 8.5 Hz, 2H), 8.15 (s, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.13 (dd, *J* = 9.0, 4.3 Hz, 1H).

3-(4-Nitrophenyl)imidazo[1,2-*b*]pyridazine (56)[15b] 4-Bromonitrobenzene (0.202 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.178 g, 1.5 mmol) affords **56** in 96% (0.230 g) yield as a yellow solid: mp 207-209 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ 8.6 (dd, *J* = 4.3, 1.3 Hz, 1H), 8.52 (d, *J* = 8.9 Hz, 2H), 8.42 (s, 1H), 8.33 (d, *J* = 8.9 Hz, 2H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.37 (dd, *J* = 8.2, 4.3 Hz, 1H).

3-(4-Chlorophenyl)imidazo[1,2-*b*]pyridazine (57)[15b] 4-Bromochlorobenzene (0.191 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.178 g, 1.5 mmol) affords **57** in 93% (0.213 g) yield as a yellow solid: mp 144-146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, *J* = 4.0 Hz, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 8.07 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.15 (dd, *J* = 9.0, 4.0 Hz, 1H).

3-(4-Methoxyphenyl)imidazo[1,2-*b*]pyridazine (58)[15b] 4-Bromoanisole (0.187 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.178 g, 1.5 mmol) affords **58** in 90% (0.202 g) yield as a yellow solid: mp 76-78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (dd, *J* = 4.4, 1.4 Hz, 1H), 8.00 (dd, *J* = 9.1, 1.4 Hz, 1H), 7.98-7.92 (m, 3H), 7.06-6.98 (m, 3H), 3.85 (s, 3H).

2-(Imidazo[1,2-*b*]pyridazin-3-yl)benzonitrile (59)[15b] 2-Bromobenzonitrile (0.182 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.178 g, 1.5 mmol) affords **59** in 96% (0.211 g) yield as a yellow solid: mp 214-216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (dd, *J* = 4.2, 1.0 Hz, 1H), 8.23 (s, 1H), 8.18 (dd, *J* = 9.2, 1.3 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.75 (td, *J* = 7.8, 1.3 Hz, 1H), 7.54 (t, *J* = 7.7, 1.0 Hz, 1H), 7.23 (dd, *J* = 9.2, 4.2 Hz, 1H).

3-(Pyridin-3-yl)imidazo[1,2-*b*]pyridazine (60)[15b] 3-Bromopyridine (0.158 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.178 g, 1.5 mmol) affords **60** in 88% (0.172 g) yield as a yellow solid: mp 112-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.23 (d, *J* = 1.8 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.46-8.36 (m, 2H), 8.10 (s, 1H), 8.02 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.09 (dd, *J* = 9.2, 4.4 Hz, 1H).

Acknowledgments

We thank CNRS and ANR for financial support.

Keywords: Palladium • Heterogeneous catalysis • Direct arylation • C-H bond activation • Atom economy • Green solvents

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10.1002/adsc.201800596

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Pd/C as Heterogeneous Catalyst for Direct Arylation of Heteroaromatics with Aryl Bromides