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FULL PAPER

Environmentally-Safe Conditions for the Palladium-Catalyzed Direct C3-Arylation with High Turn Over Frequency of Imidazo[1,2-*b*]pyridazines Using Aryl Bromides and Chlorides

Sabah Chikhi,[a,b] Safia Djebbar,[b] Jean-François Soulé,*[a] and Henri Doucet*[a]

Abstract: Phosphine-free Pd(OAc)$_2$ was found to catalyze very efficiently the direct arylation of imidazo[1,2-*b*]pyridazine at C3 position under a very low catalyst loading. The reaction can be performed employing as little as 0.1–0.05 mol% catalyst with wide range of aryl bromides in very high TOFs and TONs. In addition, some electron-deficient aryl chlorides were also found to be suitable substrates. Moreover, 31 examples of those couplings were reported using green, safe and renewable solvents such as pentan-1-ol, diethylcarbonate or cyclopentyl methyl ether, without loss of efficiency.

Introduction

In recent years, the Pd-catalyzed direct arylation of several heteroaromatics using aryl halides, *via* a C−H bond activation, has become one of the most environmentally friendly methods for the C-C bond formation.[1] Indeed, compared to other classical Pd-catalyzed reactions such as Stille, Suzuki or Negishi couplings, they do not require the preliminary synthesis of organometallic derivatives, and only HX associated to a base is generated as by-product. However, many challenge remains in order to get sustainable reaction conditions. For example, the major drawback of most of the described procedures is that they generally require 5-10 mol% palladium catalyst associated to 10–20 mol% of phosphine ligands. Since the discovery by de Vries and co-workers that only trace amount of phosphine-free catalyst Pd(OAc)$_2$ (i.e., 0.1−0.01 mol%) are able to catalyze Heck and Suzuki reactions[2] –due to the soluble palladium(0) clusters formation at elevated temperature– this technology has been largely employed to promote the arylation of heteroarenes.[3] An additional drawback of Pd-catalyzed direct arylation in terms of green chemistry is that they often employ DMF or DMA as toxic or non-renewable solvents. According to the solvent selection guides published by chemical companies, DMF or DMA should be replaced by more sustainable solvents.[4] Some reports demonstrated that C–H bond arylation could be conducted in carbonates,[5] such as diethylcarbonate (DEC), which is a polar, aprotic, nontoxic, and biodegradable solvent.[6] Cyclopentyl methyl ether (CPME) is also a suitable alternative solvent for C–H bond activation/functionalization.[7] Highly polar and protic solvents, such as alcohols[8] or water,[9] have also been used in transition metal-catalyzed C–H bond activation. However, the merging of low loading phosphine-free palladium catalyst conditions with eco-friendly or bio-sourced solvent remains a challenge, especially with aryl chlorides.

As a continuation of our researches on the development of environmentally-safe conditions for the Pd-catalyzed direct arylation, and based on our previous work on direct arylation of imidazo[1,2-a]pyridine,[3d] which displayed a very high reactivity, we turned our attention to the reactivity of imidazo[1,2-*b*]pyridazine in direct arylation. Such heterocycles have potential applications in medicinal chemistry. As examples, the 3-arylimidazo[1,2-*b*]pyridazine scaffold displays selective inhibition of Mps1 (TTK) Kinase.[10] In 2010, Berteina-Raboin, Guillaumet and co-workers described the first and unique example of direct arylations of 6-chloroimidazo[1,2-*b*]pyridazine with aryl bromides.[11] They reported that the use of 10 mol% Pd(OAc)$_2$ associated to 20 mol% PPh$_3$ in toluene promotes efficiently such couplings in good yields. Due to the important biological properties of 3-arylimidazo[1,2-*b*]pyridazines, the discovery of more environmentally-safe conditions for the direct coupling of imidazo[1,2-*b*]pyridazine derivatives with aryl bromides, especially using low loadings of a phosphine-free catalyst in renewable solvents, would be a considerable advantage for industrial applications.
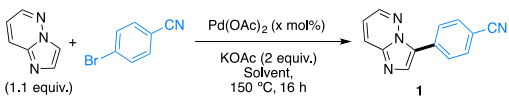
Results and Discussion

Imidazo[1,2-*b*]pyridazine and 4-bromobenzonitrile were used as model substrates, and we choose our previously described optimized reaction conditions for the direct arylation of imidazo[1,2-*a*]pyridine (*i.e.*, Pd(OAc)$_2$ as catalyst, 2 equivalents of KOAc, in DMA at 150 ºC) (Table 1).[3d] We found that the C3 arylated product **1** was obtained in very high yield using only 1 mol% of Pd(OAc)$_2$ without phosphine ligand (Table 1, entry 1). The TONs of the reaction were increased to 1940 and 8900 using 0.05 or 0.01 mol% catalyst loadings, respectively (Table 1, entries 2-4). In order to discover safer reaction conditions, we decided to evaluate greener solvents for this coupling using 0.05 mol% of Pd(OAc)$_2$. Pentan-1-ol, DEC, and CPME allowed the formation of desired product **1** in high yields (Table 1, entries 6, 8, and 10). As the association of palladium salts to pyridine derivatives as ligands provides in some cases very efficient

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catalysts for direct arylation reactions,[12] we also performed a comparison study using 1,10-phenanthroline as ligand (Table 1, entries 5, 7, 9 and 11). In all cases, the addition of 0.05 mol% of 1,10-phenanthroline to the reaction mixture did not allowed any yield improvement or change in the regioselectivity. We also performed the reaction at a lower temperature of 100 ºC (Table 1, entries 12-14). However, lower TONs were obtained whatever the employed solvent. As expected, in the absence of Pd(OAc)$_2$ catalyst, no reaction occurred (Table 1, entry 15). It is important to note that all the reactions which employed 0.05 or 0.01 mol% catalyst were performed using new Schlenk tubes and new stirring bars to avoid contamination by palladium residues.

Table 1. Influence of the Reaction Conditions

Entry	(x mol %)	Solvent	Conv. (%)[a]	Yield in 1 (%)[b]	TON
1	1	DMA	100	98	98
2	0.5	DMA	100	98	196
3	0.05	DMA	100	97	1940
4	0.01	DMA	92	89	8900
5[c]	0.05	DMA	69	65	1300
6	0.05	pentan-1-ol	100	97	1940
7[c]	0.05	pentan-1-ol	0	0	0
8	0.05	DEC	100	90	1900
9[c]	0.05	DEC	78	78	1560
10	0.05	CPME	100	96	1920
11[c]	0.05	CPME	38	36	720
12[d]	0.5	DMA	67	66	132
13[d]	0.5	pentan-1-ol	37	37	74
14[d]	0.5	DEC	71	68	136
15	0	DMA	–	–	–

[a] Based on 4-bromobenzonitrile consumption using GC-MS analysis with dodecane as internal standard. [b] Isolated yield. [c] In the presence of 0.05 mol% of 1,10-phenanthroline. [d] Reaction performed at 100 ºC.

As full consumption of 4-bromobenzonitrile was observed in all cases in the presence of 0.05 mol% catalyst using DMA, DEC, CPME, or pentan-1-ol, we decided to plot a TON versus time of this model reaction with the different solvents (Figure 1a). Remarkably, all the solvents were compatible under our standard catalytic conditions (0.05 mol% Pd(OAc)$_2$, KOAc (2 equiv.) at 150 ºC), but clear differences among them were

evident. The reaction performed in CPME was the slowest for the formation of arylated product **1** (TOF^{10min} = 3000 h^{-1}), albeit the reaction was complete after 2 h. Pentan-1-ol displayed a higher efficiency, as a TOF^{10min} of 5040 h^{-1} was obtained after 10 minutes. The reaction performed in DEC indicated a TOF^{10min} of 7560 h^{-1} after 10 minutes. The highest TOF after 10 minutes was obtained when the reaction was performed in DMA, with complete conversion after only 30 minutes and a TOF^{10min} of 10320 h^{-1} after 10 minutes. Similar experiments were conducted with electron-rich 4-bromoanisole (Figure 1b). With all solvents conditions, the desired C3-arylated imidazo[1,2-b]pyridazine **2** was obtained, but again marked differences were observed. Again, the reaction in DMA was the most efficient to deliver the coupling product **2**, although a lower TOF^{10min} of 2760 h^{-1} than with 4-bromobenzonitrile was obtained. The reaction performed in pentan-1-ol also displayed a high TOF (TOF^{10min} = 1920 h^{-1}); whereas, in DEC or CPME the reactions were not complete after 5 h, with conversions of 80% and 42%, respectively and lower TOFs^{10min} of 960 h^{-1} and 480 h^{-1}.
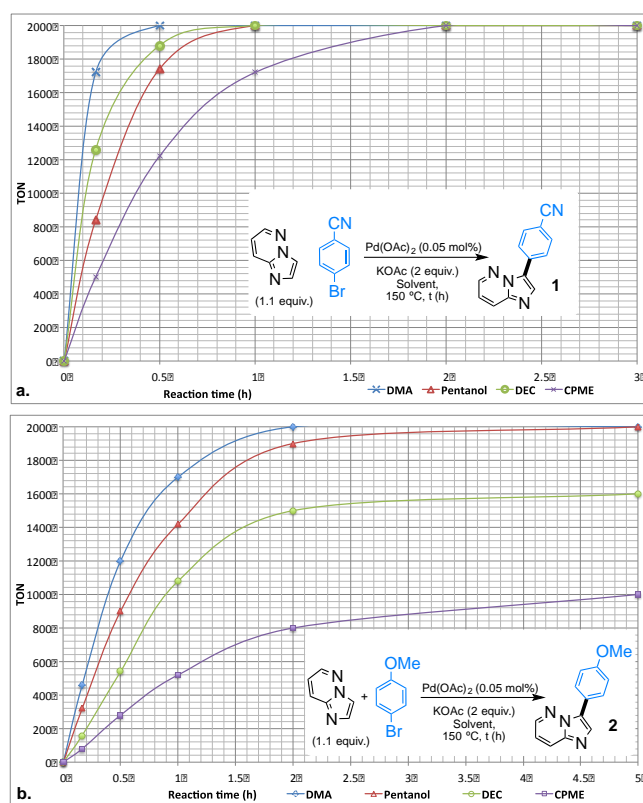

Figure 1. TON *vs* Time of Pd-Catalyzed Coupling Reactions between Imidazo[1,2-b]pyridazine in Different Solvents: a) with 4-bromobenzonitrile or b) with 4-bromoanisole.

With these catalytic systems in hands, we decided to investigate the scope of aryl bromides in the Pd-catalyzed direct C3-arylation of imidazo[1,2-b]pyridazine using a low loading of phosphine-free palladium catalyst (i.e., Pd(OAc)$_2$ 0.05 mol%) (Scheme 1). As seen above, 4-bromoanisole reacted nicely with

imidazo[1,2-*b*]pyridazine to give the arylated heterocycle **2** in 79% isolated yield. Bromobenzenes *para*-substituted by nitro, formyl or acetyl groups gave the C3-arylated products **3-5** in high yields in both DMA and pentan-1-ol. Ethyl 4-bromobenzoate was also tolerated by the optimized reaction conditions to afford **6** in 91% yield. Using solvent free-conditions, a slightly lower yield of 51% was obtained. Chloro or fluoro substituents at *para*-position of bromobenzene have almost no effect on the reaction, as the coupling products **7** and **8** were isolated in 89% and 93% yields, respectively. The reaction with 4-bromotoluene as coupling partner smoothly proceeded in DMA or in pentan-1-ol to afford the coupling product **9** in 82% or 78% yield. Interestingly, 4-iodoaniline, which is a very electron-rich substrate, was also tolerated to afford the heterocycle **10** in 91%; whereas, 4-bromoaniline was unreactive. It is important to note that the direct arylation proceeded faster than amination reaction.[13] The reaction performed in pentan-1-ol instead of DMA led to a lower yield of 58% in **10**. *Meta*-substituted aryl bromides reacted with imidazo[1,2-*b*]pyridazine in the same line than the *para*-substituted ones. As examples, methyl 3-bromobenzoate and 3-bromoacetophenone gave the desired coupling products **11** and **12** in excellent yields in DMA or pentan-1-ol. 1,3-Dibromobenzene could be used for the selective mono-heteroarylation, affording 3-(3-bromophenyl)imidazo[1,2-*b*]pyridazine **13**, in which one C–Br bond remained untouched and could be used in further Pd-catalyzed reactions. 3-Iodoaniline was nicely coupled with imidazo[1,2-*b*]pyridazine in DMA to afford **14** in 82% yield without amination as side-reaction. A very electron-deficient aryl bromide, such as 3,5-bis(trifluoromethyl)bromobenzene, was also tolerated by the optimized conditions to afford the arylated heterocycle **15** in 90% yield. The reaction seems to be insensitive to the steric hindrance. Indeed, aryl bromides bearing 2-cyano, 2-formyl or 2-trifluoromethyl substituents nicely reacted to afford **16-18** in good yields. Notably, such *ortho*-substituted aryl bromides could be coupled in pentan-1-ol without loss of efficiency. From 1- bromonaphthalene or 1-bromopyrene, the C3 polycyclic hydrocarbons substituted imidazo[1,2-*b*]pyridazine **19** and **20** were isolated in 74% and 79% yields, respectively. Heteroaryl bromides, such as 3-bromoquinoline, 3-bromopyridine and 5-bromopyrimidine were also successfully coupled to give the heterocycle dyads **21-23** in 73-94% yields. Again, these reactions could be performed in pentan-1-ol or CPME instead of DMA. We also demonstrated that the coupling products could be isolated by recrystallization in cyclohexane after simple removal of DMA (e.g., **3**, **5**, **15**, and **18** in scheme 1), instead of silica gel column chromatography, affording a very environmentally-attractive procedure for the synthesis of such compounds.
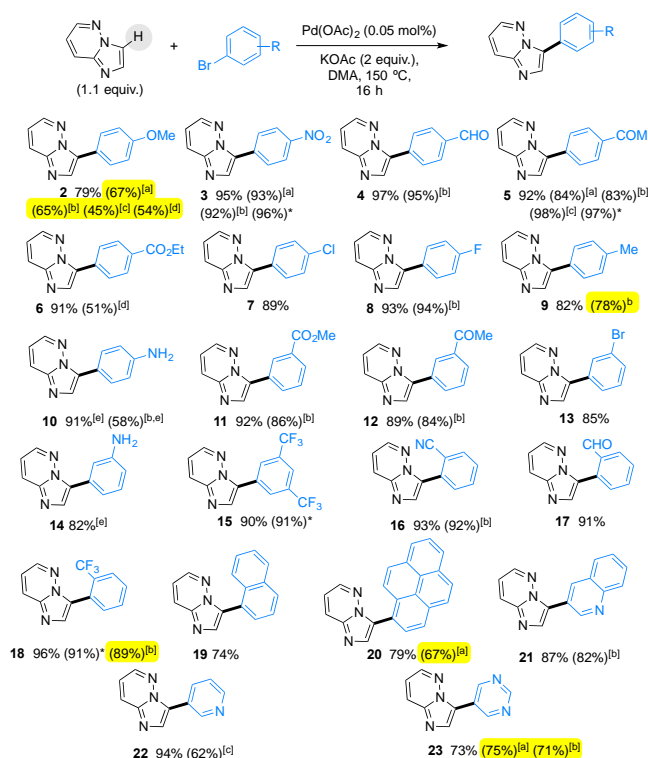
Scheme 1. Scope of Aryl Bromides in Pd-Catalyzed Direct Arylation of Imidazo[1,2-*b*]pyridazine. [a] Reaction performed in DEC instead of DMA. [b] Reaction performed in pentan-1-ol instead of DMA. [c] Reaction performed in CPME instead of DMA. [d] Reaction performed under neat conditions. [e] Reaction performed from ArI instead of ArBr. * Reaction performed on 10 mmol scale; after removal of DMA under vacuo, the product was isolated by simple recrystallization in cyclohexane.

Having successfully coupled a wide range of aryl bromides with imidazo[1,2-*b*]pyridazine, we next investigated the efficiently of this simple catalytic system –namely, phosphine-free Pd(OAc)$_2$ in the presence of KOAc– to promote direct arylation using aryl chlorides. Rare use has been made of (hetero)aryl chlorides in Pd-catalyzed direct arylations, despite the fact that among aryl halides, aryl chlorides exhibit the wider diversity of available compounds at an affordable cost. In most cases, expensive ligands or catalytic systems should be used to overcome their poor reactivity in Pd-catalyzed direct arylation.[14] Only a few reports focused on the use of phosphine-free palladium catalyts.[3e, 15] First, we decided to evaluate several solvents for this coupling using 4-chlorobenzonitrile as aryl source in the presence of 0.1 mol% of Pd(OAc)$_2$ and 2 equivalents of KOAc as base without any additive (Figure 2). Interestingly, a full conversion was observed in DMA after 2 h with a TOF^{30min} of 840 h^{-1} after 30 minutes. The reaction was more sluggish in other solvents such as pentan-1-ol or DEC, but full conversions could be reached after 6 h. It is important to note that DEC has been previously used as eco-friendly solvent in Pd-catalyzed direct arylation of several heteroarenes in the presence of aryl chlorides as aryl source, but diphosphine ligands were added to the reaction mixture.[16] To the best of our knowledge, this is one of the rare examples of merging phosphine-free palladium

catalyst with eco-friendly or bio-sourced solvents for the direct arylation of heteroarenes using aryl chlorides as aryl source. On the contrary, CPME as solvent was almost ineffective for this transformation.
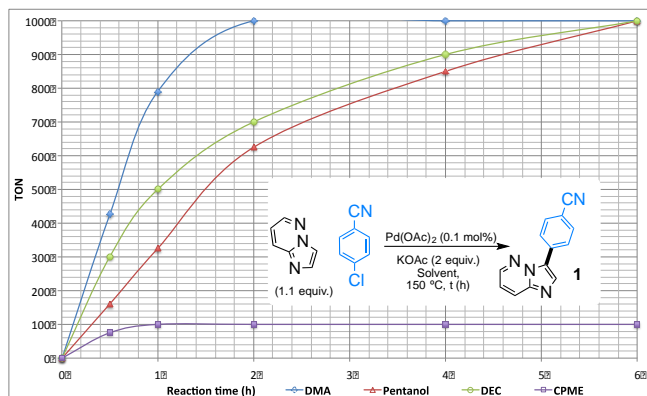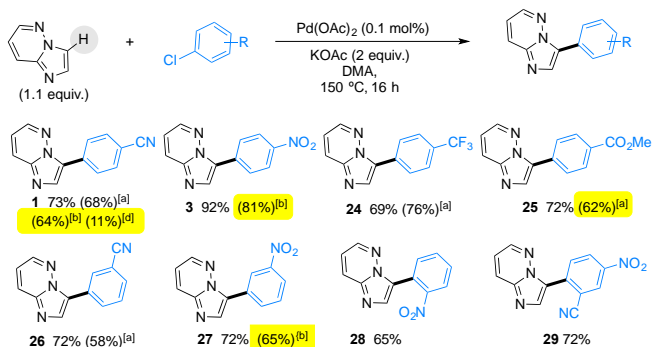

Figure 2. TON *vs* Time of Pd-Catalyzed Coupling Reaction Between Imidazo[1,2-*b*]pyridazine with 4-Chloronitrobenzene in Different Solvents.

Having found effective conditions for the use of activated aryl chlorides, namely, 0.1 mol% of Pd(OAc)$_2$ in the presence of 2 equivalents of KOAc in DMA, we turned our attention to the aryl chloride scope for these Pd-catalyzed C–H bond arylations. Chlorobenzenes substituted by electron-withdrawing groups at *para*-position such as CN, NO$_2$, CF$_3$, CO$_2$Me allowed the synthesis of the 3-arylated imidazo[1,2-*b*]pyridazines **1**, **3**, **24** and **25** in 69-92% yields. From 3-chlorobenzonitrile and 3-chloronitrobenzene, the coupling products **26** and **27** were isolated in excellent yields. Under the same conditions, the reaction proceeded smoothly in the presence of *ortho*-substituted aryl chlorides. For examples, from 2-chloronitrobenzene or 2-chloro-5-nitrobenzonitrile, the C3 arylated products **28** and **29** were obtained in 65% and 72% yields, respectively. Some of these couplings were also successfully performed in DEC and pentan-1-ol as alternative sustainable solvents. However, aryl chlorides bearing an electron-donating substituent (e.g., OMe or Me) were unreactive under these phosphine-free conditions.

In addition, we investigated the Pd-catalyzed direct arylation of 6-chloroimidazo[1,2-*b*]pyridazine in environmentally-safe conditions, namely 0.1 mol% Pd(OAc)$_2$ associated to KOAc as base in pentan-1-ol. Electron-poor *para*-substituted aryl bromides, such as 4-bromonitrobenzene and 4-bromobenzaldehyde, gave the coupling products **30** and **31** in 78% and 82% yields, respectively. Notably, the reaction could also be performed from 4-chloronitrobenzene to afford **30** in a similar yield, albeit DMA should be used as solvent. The reaction with 1,4-dibromobenzene selectively gave the monoarylated product **32** in 75% yield, which contains a C–Br bond allowing further transformations. A second direct arylation from **32** via the activation of its C–Br bond was not observed. This poor reactivity is due to a slow oxidative addition of **32** to palladium owing the electron-donor character of the first introduced heteroarene. Bulky aryl bromides, such as methyl 2-bromobenzoate and 1-bromonaphthalene, were also tolerated by the optimized environmentally-safe conditions to afford the products **33** and **34** in 59% and 76% yields, respectively. Heteroaryl bromides have also been successfully coupled with 6-chloroimidazo[1,2-*b*]pyridazine to offer **35** and **36** in good yields. In all cases, no cleavage of the imidazopyridazine C–Cl bond was observed. This chemoselectivity might be explained by the poor reactivity of electron-rich aryl chlorides under phosphine-free palladium conditions.
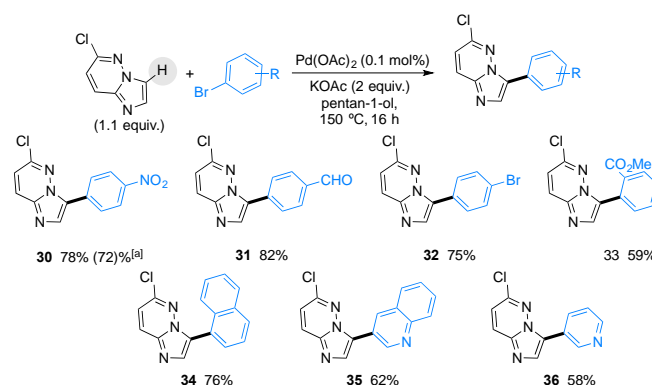
Scheme 3. Scope of Aryl Bromides and Chlorides in Pd-Catalyzed Direct Arylation of 6-Chloroimidazo[1,2-*b*]pyridazine. [a] The reaction was performed from 4-chloronitrobenzene instead of 4-bromonitrobenzene, and DMA was used as solvent instead of pentan-1-ol.

Finally, we investigated the synthesis of 2,3-diarylimidazo[1,2-*b*]pyridazine derivatives (Scheme 4). From 3-(4-fluorophenyl)imidazo[1,2-*b*]pyridazine **8**, we attempted to functionalize directly the C2 position through Pd-catalyzed direct arylation. However, this synthetic scheme failed. Hence, we considered a two steps synthesis involving the preparation of 2-bromo-3-(4-fluorophenyl)imidazo[1,2-*b*]pyridazine **37**

intermediate. From aryl bromide derivative **37**, classical Suzuki reaction conditions using phenylboronic acid or 3-thienylboronic acid as coupling partners allowed the formation of 2,3-diarylimidazo[1,2-*b*]pyridazines **38** and **39** in 86% and 89% yields, respectively.
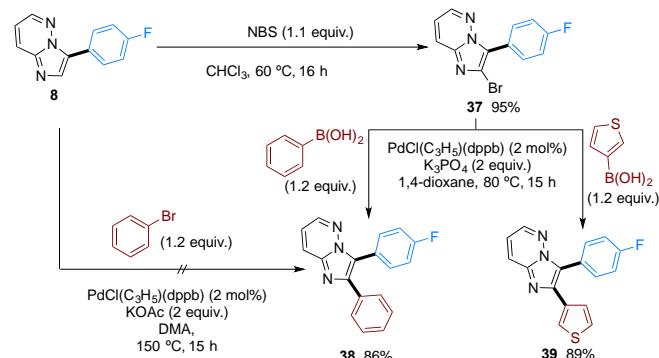
Scheme 4. Examples of Synthesis of 2,3-Diarylimidazo[1,2-*b*]pyridazine Derivatives..

Conclusions

In summary, we have developed environmentally-safe conditions for the direct C3 arylation of imidazo[1,2-*b*]pyridazines. We found that the reaction proceed with very high TOFs and TONs using as little as 0.1–0.05 mol% of phosphine-free Pd(OAc)$_2$ as catalyst precursor. With this procedure, there is no need to eliminate phosphine residues at the end of the reaction. In addition, for several examples (i.e., 31 compounds over 36), we demonstrated that DMA, which is a toxic solvent, can be successfully substituted by eco-friendly or bio-resourced solvents, such as pentan-1-ol and diethylcarbonate, providing a greener approach to the synthesis of 3-aryl imidazo[1,2-*b*]pyridazines. The reaction conditions allowed the use of a wide variety of substituents on the aryl bromide such as ester, acetyl, formyl, propionyl, benzoyl, nitro, nitrile, bromo, chloro, fluoro, methoxy and amino. In addition, heteroaryl bromides could also employed. Moreover, some electron-deficient aryl chlorides, which are very attractive substrates in terms of atom-economy and cost, have been used instead of aryl bromides with comparable yields.

Experimental Section

All reactions were carried out under argon atmosphere with standard Schlenk techniques. 1,4-Dioxane, DMA, diethylcarnonate and pentan-1-ol were purchased from Acros Organics and were not purified before use. ^{1}H NMR spectra were recorded on Bruker GPX (400 MHz) spectrometer. Chemical shifts (δ) were reported in parts per million relative to residual DMSO (2.50 ppm (quintet, J_{HD}=1.9 Hz) ppm for ^{1}H; 39.52 ppm for ^{13}C), constants were reported in Hertz. ^{1}H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ^{13}C NMR

spectra were recorded at 100 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

Preparation of the PdCl(dppb)(C$_3$H$_5$) catalyst:[17] An oven-dried 40-mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with [Pd(C$_3$H$_5$)Cl]$_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The yellow powder was used without purification. ^{31}P NMR (81 MHz, CDCl$_3$) δ (ppm) = 19.3 (s).

General Procedure. As a typical experiment, the reaction of the aryl halides (1 mmol), imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol) or 6-chloroimidazo[1,2-*b*]pyridazine (0.169 g, 1.1 mmol), and KOAc (0.196 g, 2 mmol) at 150 °C over 16 h in 4 mL of a freshly prepared solution of solvent (see tables or schemes) which contains the appropriate amount of Pd(OAc)$_2$ (see preparation of this solution below), under argon affords the coupling product after evaporation of the solvent and purification on silica gel or recrystallization in cyclohexane.

A solution of Pd(OAc)$_2$ was freshly prepared using 2.8 mg of Pd(OAc)$_2$ (0.0125 mmol) and 100 mL of the appropriate solvent (DMA, pentan-1-ol, DEC, or CPME) under argon."

4-(Imidazo[1,2-*b*]pyridazin-3-yl)benzonitrile (1): Following the general procedure using 4-bromobenzonitrile (0.182 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 70:30) to afford the desired compound **1** (0.216 g, 98%) as a yellow solid (mp = 156-158 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.71 (dd, J = 1.6 and 4.5 Hz, 1H, H6), 8.49 (s, 1H, H2), 8.42 (d, J = 8.5 Hz, 2H), 8.27 (dd, J = 1.6 and 9.2 Hz, 1H, H8), 7.97 (d, J = 8.5 Hz, 2H), 7.38 (dd, J = 4.5 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 144.3, 140.9, 134.7, 132.9, 132.6, 126.3, 126.1, 125.5, 118.9, 118.1, 109.5. Elemental analysis: calcd (%) for C$_{13}$H$_8$N$_4$ (220.23): C 70.90, H 3.66; found: C 71.19, H 3.86.

3-(4-Methoxyphenyl)imidazo[1,2-*b*]pyridazine (2): Following the general procedure using 4-bromoanisole (0.187 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 70:30) to afford the desired compound **2** (0.178 g, 79%) as a yellow solid (mp = 75-79 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.59 (dd, J = 1.6 and 4.4 Hz, 1H, H6), 8.20-8.15 (m, 2H, H2 and H8), 8.05 (d, J = 8.9 Hz, 2H), 7.23 (dd, J = 4.4 and 9.2 Hz, 1H, H7), 7.06 (d, J = 8.9 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 158.8, 143.7, 139.3, 131.8, 127.8, 127.3, 125.9, 120.9, 116.5, 114.1, 55.1. Elemental analysis: calcd (%) for C$_{13}$H$_{11}$N$_3$O (225.25) C 69.32, H 4.92; found: C 69.58, H 5.17.

3-(4-Nitrophenyl)imidazo[1,2-*b*]pyridazine (3): Following the general procedure using 4-bromonitrobenzene (0.200 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 55:45) to afford the desired compound **3** (0.228 g, 95%) as a yellow solid (mp = 207-210 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.76 (dd, J = 1.7 and 4.4 Hz, 1H, H6), 8.57 (s, 1H, H2), 8.52 (d, J = 8.9 Hz, 2H), 8.37 (d, J = 8.9 Hz, 2H), 8.31 (dd, J = 1.7 and 9.1 Hz, 1H, H8), 7.42 (dd, J = 4.4 and 9.1 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 145.8, 144.4, 141.2, 135.3, 134.9, 126.5, 126.4, 126.3, 124.1, 118.5. Elemental analysis: calcd (%) for C$_{12}$H$_8$N$_4$O$_2$ (240.22): C 60.00, H 3.36; found: C 59.79, H 3.48.

4-(Imidazo[1,2-*b*]pyridazin-3-yl)benzaldehyde (4): Following the general procedure using 4-bromobenzaldehyde (0.183 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by

flash chromatography on silica gel (pentane-Et$_2$O, 65:35) to afford the desired compound **4** (0.217 g, 97%) as a yellow solid (mp = 138-141 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 9.98 (s, 1H), 8.66 (d, J = 4.4 Hz, 1H, H6), 8.43 (s, 1H, H2), 8.37 (d, J = 8.2 Hz, 2H), 8.22 (d, J = 9.2 Hz, 1H, H8), 7.96 (d, J = 8.2 Hz, 2H), 7.33 (dd, J = 4.4 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 192.6, 144.5, 141.2, 125.1, 135.0, 134.4, 130.2, 126.6, 126.4, 126.3, 118.3. Elemental analysis: calcd (%) for C$_{13}$H$_9$N$_3$O (223.24): C 69.95, H 4.06; found: C 70.12, H 4.21.

1-(4-(Imidazo[1,2-*b*]pyridazin-3-yl)phenyl)ethan-1-one (5): Following the general procedure using 4-bromoacetophenone (0.199 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 65:35) to afford the desired compound **5** (0.218 g, 92%) as a yellow solid (mp = 136-138 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.71 (dd, J = 1.6 and 4.4 Hz, 1H, H6), 8.45 (s, 1H, H2), 8.36 (d, J = 8.4 Hz, 2H), 8.26 (dd, J = 1.6 and 9.2 Hz, 1H, H8), 8.08 (d, J = 8.4 Hz, 2H), 7.36 (dd, J = 4.4 and 9.2 Hz, 1H, H7), 2.62 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 197.2, 144.2, 140.6, 135.4, 134.3, 132.8, 128.7, 126.3, 126.2, 125.7, 117.8, 26.7. Elemental analysis: calcd (%) for C$_{14}$H$_{11}$N$_3$O (237.26): C 70.87, H 4.67; found: C 71.13, H 4.51.

Ethyl 4-(imidazo[1,2-*b*]pyridazin-3-yl)benzoate (6): Following the general procedure using ethyl 4-bromobenzoate (0.229 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 65:35) to afford the desired compound **6** (0.243 g, 91%) as a pale yellow solid (mp = 108-110 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.75 (dd, J = 1.6 and 4.5 Hz, 1H, H6), 8.49 (s, 1H, H2), 8.35 (d, J = 8.5 Hz, 2H), 8.3 (dd, J = 1.9 and 9.2 Hz, 1H, H8), 8.09 (d, J = 8.5 Hz, 2H), 7.42 (dd, J = 4.5 and 9.2 Hz, 1H, H7), 4.35 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 165.4, 144.5, 140.2, 133.2, 132.6, 129.5, 128.6, 126.3, 126.0, 125.9, 118.5, 60.8, 14.2. Elemental analysis: calcd (%) for C$_{15}$H$_{13}$N$_3$O$_2$ (267.29): C 67.40, H 4.90; found: C 67.58, H 5.12.

3-(4-Chlorophenyl)imidazo[1,2-*b*]pyridazine (7): Following the general procedure using 1-bromo-4-chlorobenzene (0.191 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 65:35) to afford the desired compound **7** (0.204 g, 89%) as a pale yellow solid (mp = 144-148 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.66 (dd, J = 1.6 and 4.5 Hz, 1H, H6), 8.32 (s, 1H, H2), 8.25-8.19 (m, 3H), 7.59 (d, J = 8.5 Hz, 2H), 7.32 (dd, J = 4.5 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 144.0, 140.0, 133.2, 132.1, 128.7, 127.8, 127.3, 126.1, 126.1, 117.4. Elemental analysis: calcd (%) for C$_{12}$H$_8$ClN$_3$ (229.67): C 62.76, H 3.51; found: C 62.80, H 3.72.

3-(4-Fluorophenyl)imidazo[1,2-*b*]pyridazine (8): Following the general procedure using 1-bromo-4-fluorobenzene (0.175 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 70:30) to afford the desired compound **8** (0.200 g, 94%) as a pale yellow solid (mp = 108-111 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.64 (dd, J = 1.6 and 4.4 Hz, 1H, H6), 8.25 (s, 1H, H2), 8.23-8.15 (m, 3H), 7.36 (t, J = 8.9 Hz, 2H), 7.29 (dd, J = 4.4 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 161.5 (d, J = 244.5 Hz), 143.9, 139.7, 132.7, 128.4 (d, J = 8.2 Hz), 126.4, 126.1, 125.0 (d, J = 3.0 Hz), 117.1, 115.6 (d, J = 19.4 Hz). Elemental analysis: calcd (%) for C$_{12}$H$_8$FN$_3$ (213.22): C 67.60, H 3.78; found: C 67.69, H 3.66.

3-(*P*-tolyl)imidazo[1,2-*b*]pyridazine (9): Following the general procedure using 4-bromotoluene (0.171 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 70:30) to afford the desired

compound **9** (0.172 g, 82%) as a yellow solid (mp = 105-108 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.63 (dd, J = 1.6 and 4.5 Hz, 1H, H6), 8.22 (s, 1H, H2), 8.20 (d, J = 9.2 Hz, 1H, H8), 8.04 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.27 (dd, J = 4.7 and 9.2 Hz, 1H, H7), 2.36 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 143.8, 139.6, 137.2, 132.4, 129.2, 127.3, 126.2, 126.0, 125.6, 116.8, 20.9. Elemental analysis: calcd (%) for C$_{13}$H$_{11}$N$_3$ (209.25) C 74.62, H 5.30; found: C 74.97, H 5.46.

4-(Imidazo[1,2-*b*]pyridazin-3-yl)aniline (10): Following the general procedure using 4-iodoaniline (0.219 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$-MeOH, 98:2) to afford the desired compound **10** (0.191 g, 91%) as a yellow solid (mp = 150-152 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.57 (dd, J = 1.6 and 4.5 Hz, 1H, H6), 8.13 (dd, J = 1.9 and 9.2 Hz, 1H, H8), 8.11 (s, 1H, H2), 7.80 (d, J = 8.5 Hz, 2H), 7.18 (dd, J = 4.7 and 9.2 Hz, 1H, H7), 6.69 (d, J = 8.5 Hz, 2H), 5.37 (brs, 2H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 148.7, 143.4, 138.8, 130.8, 128.4, 127.5, 115.8, 115.7, 113.6. Elemental analysis: calcd (%) for C$_{12}$H$_{10}$N$_4$ (210.24) C 68.56, H 4.79; found: C 68.84, H 4.56.

Methyl 3-(imidazo[1,2-*b*]pyridazin-3-yl)benzoate (11): Following the general procedure using methyl 3-bromobenzoate (0.215 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 70:30) to afford the desired compound **11** (0.233 g, 92%) as a pale yellow solid (mp = 119-121 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.78 (s, 1H), 8.69 (dd, J = 1.7 and 4.6 Hz, 1H, H6), 8.38 (d, J = 7.8 Hz, 1H), 8.36 (s, 1H, H2), 8.24 (dd, J = 1.7 and 9.2 Hz, 1H, H8), 7.96 (ddd, J = 6.1, 6.4 and 7.8 Hz, 1H), 7.67 (dd, J = 7.5 and 7.8Hz, 1H), 7.33 (dd, J = 4.4 and 9.2 Hz, 1H, H7), 3.90 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 166.1, 144.1, 140.1, 133.4, 130.9, 130.1, 129.2, 129.0, 128.3, 126.5, 126.2, 117.5, 52.3. Elemental analysis: calcd (%) for C$_{14}$H$_{11}$N$_3$O$_2$ (253.26) C 66.40, H 4.38; found: C 66.57, H 4.71.

1-(3-(Imidazo[1,2-*b*]pyridazin-3-yl)phenyl)ethan-1-one (12): Following the general procedure using 3-bromoacetophenone (0.197 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$-MeOH, 98:2) to afford the desired compound **12** (0.211 g, 89%) as a pale yellow solid (mp = 143-146 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.72 (s, 1H), 8.69 (dd, J = 1.6 and 4.5 Hz, 1H, H6), 8.39 (d, J = 7.7 Hz, 1H), 8.39 (s, 1H, H2), 8.25 (dd, J = 1.6 and 9.2 Hz, 1H, H8), 7.98 (ddd, J = 6.5, 6.7 and 7.7 Hz, 1H), 7.68 (dd, J = 7.1 and 7.4 Hz, 1H), 7.34 (dd, J = 4.4 and 9.2 Hz, 1H, H7), 2.67 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 197.8, 144.1, 140.0, 137.2, 133.4, 130.6, 129.1, 128.9, 127.4, 126.4, 126.2, 125.7, 117.5, 26.9. Elemental analysis: calcd (%) for C$_{14}$H$_{11}$N$_3$O (237.26) C 70.87, H 4.67; found: C 71.05, H 4.98.

3-(3-Bromophenyl)imidazo[1,2-*b*]pyridazine (13): Following the general procedure using 1,3-dibromobenzene (0.236 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 70:30) to afford the desired compound **13** (0.233 g, 85%) as a grey solid (mp = 92-95 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.69 (dd, J = 1.7 and 4.5 Hz, 1H, H6), 8.44 (t, J = 1.9 Hz, 1H), 8.38 (s, 1H, H2), 8.24 (dd, J = 1.7 and 9.1 Hz, 1H, H8), 8.17 (ddd, J = 6.1, 6.7 and 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.48 (dd, J = 7.1 and 7.4 Hz, 1H), 7.33 (dd, J = 4.5 and 9.1 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 144.1, 140.2, 133.6, 130.8, 130.7, 130.3, 128.2, 126.2, 125.6, 125.0, 122.0, 117.6. Elemental analysis: calcd (%) for C$_{12}$H$_8$BrN$_3$ (274.12) C 52.58, H 2.94; found: C 52.67, H 3.14.

3-(Imidazo[1,2-*b*]pyridazin-3-yl)aniline (14): Following the general procedure using 3-iodoaniline (0.219 g, 1 mmol) and imidazo[1,2-

b]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$-MeOH, 98:2) to afford the desired compound **14** (0.172 g, 82%) as a brown solid (mp = 112-115 ºC). ^{1}H NMR (400 MHz, d_6-DMSO**)** δ (ppm) 8.61 (dd, *J* = 1.6 and 4.5 Hz, 1H, H6), 8.18 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 8.08 (s, 1H, H2), 7.35 (dd, *J* = 2.0 and 2.1 Hz, 1H), 7.29-7.20 (m, 2H), 7.14 (dd, *J* = 7.5 and 7.6 Hz, 1H), 6.6 (md, *J* = 7.9 Hz, 1H), 5.20 (brs, 2H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 148.8, 143.7, 139.5, 132.4, 129.1, 128.8, 128.1, 125.9, 116.7, 114.3, 113.6, 111.7. Elemental analysis: calcd (%) for C$_{12}$H$_{10}$N$_4$ (210.24) C 68.56, H 4.79; found: C 68.79, H 4.89.

3-(3,5-Bis(trifluoromethyl)phenyl)imidazo[1,2-*b*]pyridazine (15): Following the general procedure using 3,5-bis(trifluoromethyl)bromobenzene (0.293 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 70:30) to afford the desired compound **15** (0.298 g, 90%) as a grey solid (mp = 156-159 ºC). ^{1}H NMR (400 MHz, d_6-DMSO**)** δ (ppm) 8.88 (s, 2H), 8.77 (dd, *J* = 1.6 and 4.5 Hz, 1H, H6), 8.66 (s, 1H), 8.29 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 8.06 (s, 1H, H2), 7.4 (dd, *J* = 4.5 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 141.2, 140.6, 134.8, 130.9, 128.4 (q, *J* = 44.9 Hz), 125.6, 124.6, 124.0, 123.1 (q, *J* = 272.1 Hz), 120.2, 118.1. Elemental analysis: calcd (%) for C$_{14}$H$_7$F$_6$N$_3$ (331.22) C 50.77, H 2.13; found: C 50.98, H 2.08.

2-(Imidazo[1,2-*b*]pyridazin-3-yl)benzonitrile (16): Following the general procedure using 2-bromobenzonitrile (0.182 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 70:30) to afford the desired compound **16** (0.205 g, 93%) as a grey solid (mp = 214-218 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.62 (dd, *J* = 1.6 and 4.5 Hz, 1H, H6), 8.28 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 8.18 (s, 1H, H2), 8.04 (d, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.88 (dd, *J* = 7.6 and 7.8 Hz, 1H), 7.66 (d, *J* = 7.6 and 7.8 Hz, 1H), 7.38 (dd, *J* = 4.4 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 144.0, 139.7, 134.3, 133.7, 133.3, 131.1, 130.5, 129.1, 126.2, 124.4, 118.5, 118.1, 111.3. Elemental analysis: calcd (%) for C$_{13}$H$_8$N$_4$ (220.23): C 70.90, H 3.66; found: C 71.03, H 3.52.

2-(Imidazo[1,2-*b*]pyridazin-3-yl)benzaldehyde (17): Following the general procedure using 2-bromobenzaldehyde (0.183 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 65:35) to afford the desired compound **17** (0.203 g, 91%) as a grey solid (mp = 157-160 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 9.76 (s, 1H), 8.51 (dd, *J* = 1.6 and 4.4 Hz, 1H, H6), 8.24 (dd, *J* = 1.7 and 9.3 Hz, 1H, H8), 8.08 (s, 1H, H2), 8.02 (dd, *J* = 1.5 and 7.7 Hz, 1H), 7.83 (dt, *J* = 1.5 and 7.6 Hz, 1H), 7.75-7.66 (m, 2H), 7.32 (dd, *J* = 4.5 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 191.4, 144.0, 139.5, 134.5, 134.1, 133.9, 131.7, 130.0, 129.2, 128.3, 126.1, 125.2, 118.1. Elemental analysis: calcd (%) for C$_{13}$H$_9$N$_3$O (223.24): C 69.95, H 4.06; found: C 69.79, H 4.41.

3-(2-(Trifluoromethyl)phenyl)imidazo[1,2-*b*]pyridazine (18): Following the general procedure using 2-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 65:35) to afford the desired compound **18** (0.253 g, 96%) as a yellow solid (mp = 176-179 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.49 (dd, *J* = 1.5 and 4.5 Hz, 1H, H6), 8.22 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 7.94 (d, *J* = 7.7 Hz, 1H), 7.86 (s, 1H), 7.82 (dd, *J* = 6.9 and 8.7 Hz, 1H), 7.74 (dd, *J* = 6.9 and 7.7 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.3 (dd, *J* = 4.5 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 143.8, 138.7, 133.7, 133.5, 132.4, 129.8, 120.0 (q, *J* = 29.1 Hz), 126.6, 126.4 (q, *J* = 2.1 Hz), 125.8, 124.5, 123.8 (q, *J* = 274.2 Hz), 117.8. Elemental analysis: calcd (%) for C$_{13}$H$_8$F$_3$N$_3$ (263.22): C 59.32, H 3.06; found: C 59.51, H 2.85.

3-(Naphthalen-1-yl)imidazo[1,2-*b*]pyridazine (19): Following the general procedure using 1-bromonaphthalene (0.207g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 65:35) to afford the desired compound **19** (0.182 g, 74%) as a yellow solid (mp = 173-176 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.46 (dd, *J* = 1.7 and 4.4 Hz, 1H, H6), 8.27 (dd, *J* = 1.7 and 9.2 Hz, 1H, H8), 8.11-8.02 (m, 3H), 7.74 (dd, *J* = 1.6 and 7.1 Hz, 1H), 7.66 (dd, *J* = 7.1 and 7.4 Hz, 1H), 6.60-7.51 (m, 2H), 7.50-7.44 (m, 1H), 7.30 (dd, *J* = 4.4 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 143.7, 139.0, 134.0, 133.3, 131.4, 129.2, 128.9, 128.4, 126.7, 126.6, 126.2, 125.9, 125.7, 125.4, 125.3, 117.5. Elemental analysis: calcd (%) for C$_{16}$H$_{11}$N$_3$ (245.28): C 78.35, H 4.52; found: C 78.57, H 4.59.

3-(Pyren-1-yl)imidazo[1,2-*b*]pyridazine (20): Following the general procedure using 1-bromopyrene (0.281g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 80:20) to afford the desired compound **20** (0.252 g, 79%) as a yellow solid (mp = 190-194 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.50 (dd, *J* = 1.6 and 4.6 Hz, 1H, H6), 8.42 (d, *J* = 8.2 Hz, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.34-8.30 (m, 2H), 8.29-8.25 (m, 3H), 8.20 (s, 1H, H2), 8.16 (d, *J* = 9.2 Hz, 1H), 8.12 (dd, *J* = 7.4 and 7.6 Hz, 1H), 7.89 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 7.34 (dd, *J* = 4.4 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 123.7, 124.0, 124.7, 124.8, 125.4, 125.7, 126.0, 126.5, 126.8, 127.3, 128.1, 128.7, 129.2, 130.3, 130.8, 131.1, 134.6, 139.2, 143.9, 117.7, 122.9. Elemental analysis: calcd (%) for C$_{22}$H$_{13}$N$_3$ (319.36): C 82.74, H 4.10; found: C 82.89, H 3.87.

3-(Imidazo[1,2-*b*]pyridazin-3-yl)quinoline (21): Following the general procedure using 3-bromoquinoline (0.208 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 55:45) to afford the desired compound **21** (0.214 g, 87%) as a yellow solid (mp = 230-233 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 9.58 (d, *J* = 2.3 Hz, 1H), 9.20 (d, *J* = 2.4 Hz, 1H), 8.76 (dd, *J* = 1.7 and 4.4 Hz, 1H, H6), 8.58 (s, 1H, H2), 8.29 (dd, *J* = 1.7 and 9.2 Hz, 1H, H8), 8.07 (d, *J* = 3.1 and 8.2 Hz, 2H), 7.78 (ddd, *J* = 1.4, 6.8, and 8.5 Hz, 1H), 7.66 (dd, *J* = 7.0 and 8.2 Hz, 1H), 7.38 (dd, *J* = 4.5 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 148.8, 146.4, 144.3, 140.4, 133.7, 131.2, 129.6, 128.8, 128.4, 127.3, 127.3, 126.2, 124.7, 122.0, 117.9. Elemental analysis: calcd (%) for C$_{15}$H$_{10}$N$_4$ (246.27): C 73.16, H 4.09; found: C 73.27, H 4.19.

3-(Pyridin-3-yl)imidazo[1,2-*b*]pyridazine (22): Following the general procedure using 3-bromopyridine (0.157 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 55:45) to afford the desired compound **22** (0.184 g, 94%) as a grey solid (mp = 118-120 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 9.31 (d, *J* = 2.3 Hz, 1H), 8.67 (d, *J* = 4.5 Hz, 1H, H6), 8.57 (d, *J* = 5.3 Hz, 1H), 8.54 (ddd, *J* = 2.1, 7.5 and 7.7 Hz, 1H), 8.38 (s, 1H, H2), 8.25 (d, *J* = 9.2 Hz, 1H, H8), 7.54 (dd, *J* = 5.1 and 7.7 Hz, 1H), 7.33 (dd, *J* = 4.4 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 148.4, 147.1, 144.1, 140.2, 133.2, 133.2, 126.2, 124.7, 124.5, 123.6, 117.7. Elemental analysis: calcd (%) for C$_{11}$H$_8$N$_4$ (196.21): C 67.34, H 4.11; found: C 67.58, H 4.27.

3-(Pyrimidin-5-yl)imidazo[1,2-*b*]pyridazine (23): Following the general procedure using 5-bromopyrimidine (0.159 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 55:45) to afford the desired compound **23** (0.144 g, 73%) as a grey solid (mp = 230-234 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.56 (s, 2H), 9.18 (s, 1H), 8.72 (dd, *J* = 1.6 and 4.5 Hz, 1H, H6), 8.50 (s, 1H, H2), 8.29 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 7.39 (dd, *J* = 4.4 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-

DMSO) δ (ppm) 171.4, 156.9, 153.6, 144.4, 140.6, 133.8, 126.3, 123.4, 118.3. Elemental analysis: calcd (%) for $C_{10}H_7N_5$ (197.20): C 60.91, H 3.58; found: C 61.17, H 3.79.

3-(4-(Trifluoromethyl)phenyl)imidazo[1,2-*b*]pyridazine (24): Following the general procedure using 4-(trifluoromethyl)chlorobenzene (0.180 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 65:35) to afford the desired compound **24** (0.182 g, 69%) as a yellow solid (mp = 94-98 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.70 (dd, *J* = 1.6 and 4.4 Hz, 1H, H6), 8.44 (s, 1H, H2), 8.42 (d, *J* = 8.8 Hz, 2H), 8.27 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 7.87 (d, *J* = 8.5 Hz, 2H), 7.36 (dd, *J* = 4.4 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 144.3, 140.5 134.1, 132.4, 127.5 (q, *J* = 30.5 Hz), 126.3, 126.2, 125.7, 125.5 (m), 124.2 (q, *J* = 278.5 Hz), 117.8. Elemental analysis: calcd (%) for $C_{13}H_8F_3N_3$ (263.22): C 59.32, H 3.06; found: C 59.27, H 3.18.

Methyl 4-(imidazo[1,2-*b*]pyridazin-3-yl)benzoate (25): Following the general procedure using methyl 4-chlorobenzoate (0.170 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 65:35) to afford the desired compound **25** (0.182 g, 72%) as a white solid (mp = 165-167 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.70 (dd, *J* = 1.6 and 4.4 Hz, 1H, H6), 8.43 (s, 1H, H2), 8.35 (d, *J* = 8.4 Hz, 2H), 8.25 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 8.07 (d, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 4.4 and 9.2 Hz, 1H, H7), 3.88 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 165.9, 144.1, 140.6, 134.3, 132.9, 129.5, 128.1, 126.2, 126.1, 125.7, 117.8, 52.1. Elemental analysis: calcd (%) for $C_{14}H_{11}N_3O_2$ (253.26): C 66.40, H 4.38; found: C 66.49, H 4.59.

3-(Imidazo[1,2-*b*]pyridazin-3-yl)benzonitrile (26): Following the general procedure using 3-chlorobenzonitrile (0.137 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 65:35) to afford the desired compound **26** (0.159 g, 72%) as a white solid (mp = 194-198 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.72 (dd, *J* = 1.7 and 4.4 Hz, 1H, H6), 8.65 (s, 1H), 8.52 (ddd, *J* = 7.7, 7.9 and 8.0 Hz, 1H), 8.45 (s, 1H, H2), 8.26 (dd, *J* = 1.7 and 9.2 Hz, 1H, H8), 7.84 (ddd, *J* = 7.7, 7.9 and 8.0 Hz, 1H), 7.73 (d, *J* = 7.7 and 7.9 Hz, 1H), 7.37 (dd, *J* = 4.4 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 144.2, 140.4, 133.9, 131.0, 130.4, 130.0, 129.7, 129.1, 126.2, 125.1, 118.7, 117.9, 111.9. Elemental analysis: calcd (%) for $C_{13}H_8N_4$ (220.24): C 70.90, H 3.66; found: C 71.18, H 3.65.

3-(3-Nitrophenyl)imidazo[1,2-*b*]pyridazine (27): Following the general procedure using 3-chloronitrobenzene (0.157 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 55:45) to afford the desired compound **27** (0.173 g, 72%) as a yellow solid (mp = 170-174 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 9.13 (s, 1H), 8.75 (dd, *J* = 1.6 and 4.4 Hz, 1H, H6), 8.57 (d, *J* = 8.0 Hz, 1H), 8.51 (s, 1H, H2), 8.28 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 8.21 (dd, *J* = 2.5 and 8.3 Hz, 1H), 7.81 (dd, *J* = 8.0 and 8.3 Hz, 1H), 7.38 (dd, *J* = 4.5 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 148.1, 144.3, 140.5, 134.1, 132.2, 130.2, 130.0, 126.3, 125.0, 122.1, 119.8, 118.0. Elemental analysis: calcd (%) for $C_{12}H_8N_4O_2$ (240.22): C 60.00, H 3.36; found: C 60.23, H 3.57

3-(2-Nitrophenyl)imidazo[1,2-*b*]pyridazine (28): Following the general procedure using 2-chloronitrobenzene (0.157 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 55:45) to afford the desired compound **28** (0.156 g, 65%) as a yellow solid (mp = 180-185 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.47 (dd, *J* = 1.6 and 4.5 Hz,

1H, H6), 8.24 (dd, *J* = 1.6 and 9.3 Hz, 1H, H8), 8.21 (d, *J* = 8.0 Hz, 1H), 8.12 (s, 1H. H2), 7.91 (ddd, *J* = 1.5, 7.3 and 8.2 Hz, 1H), 7.82 (d, *J* = 7.3 Hz, 1H), 7.76 (ddd, *J* = 1.7, 7.3 and 8.2 Hz, 1H), 7.30 (dd, *J* = 4.4 and 9.3 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 147.6, 143.7, 139.6, 134.0, 133.2, 133.1, 130.1, 126.1, 125.0, 122.2, 118.1. Elemental analysis: calcd (%) for $C_{12}H_8N_4O_2$ (240.22): C 60.00, H 3.36; found: C 60.31, H 3.19

2-(Imidazo[1,2-*b*]pyridazin-3-yl)-5-nitrobenzonitrile (29): Following the general procedure using 2-chloro-5-nitrobenzonitrile (0.183 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.131 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 55:45) to afford the desired compound **29** (0.191 g, 72%) as a yellow solid (mp = 232-234 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.91 (d, *J* = 2.6 Hz, 1H), 8.71 (d, *J* = 4.5 Hz, 1H, H8), 8.66 (dd, *J* = 2.5 and 8.7 Hz, 1H), 8.42 (s, 1H, H2), 8.39 (d, *J* = 9.2 Hz, 1H, H6), 8.35 (dd, *J* = 1.8 and 9.2 Hz, 1H, H6), 7.47 (dd, *J* = 4.5 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 146.4, 144.5, 140.8, 138.3, 136.6, 136.0, 130.9, 129.2, 127.9, 126.5, 122.8, 119.7, 111.4. Elemental analysis: calcd (%) for $C_{13}H_7N_5O_2$ (265.23): C 58.87, H 2.66; found: C 59.11, H 2.89

6-Chloro-3-(4-nitrophenyl)imidazo[1,2-*b*]pyridazine (30): Following the general procedure using 4-bromonitrobenzene (0.200 g, 1 mmol) and 6-chloroimidazo[1,2-*b*]pyridazine (0.169 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 60:40) to afford the desired compound **30** (0.214 g, 78%) as a yellow solid (mp = 215-218 ºC). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.53 (s, 1H), 8.40-8.36 (m, 4H), 8.33 (d, *J* = 9.4 Hz, 1H), 7.52 (d, *J* = 9.4 Hz, 1H). This is a known compound and the spectral data are identical to those reported in literature.[11]

4-(6-Chloroimidazo[1,2-*b*]pyridazin-3-yl)benzaldehyde (31): Following the general procedure using 4-bromobenzaldehyde (0.183 g, 1 mmol) and 6-chloroimidazo[1,2-*b*]pyridazine (0.169 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 60:40) to afford the desired compound **31** (0.211 g, 82%) as a yellow solid (mp = 145-148 ºC). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 10.05 (s, 1H), 8.28-8.23 (m, 2H), 8.18 (s, 1H), 8.05-7.94 (m, 3H), 7.15 (d, *J* = 9.4 Hz, 1H). This is a known compound and the spectral data are identical to those reported in literature.[11]

3-(4-Bromophenyl)-6-chloroimidazo[1,2-*b*]pyridazine (32): Following the general procedure using 1,4-dibromobenzene (0.236 g, 1 mmol) and 6-chloroimidazo[1,2-*b*]pyridazine (0.169 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 60:40) to afford the desired compound **32** (0.231 g, 75%) as a yellow solid (mp = 152-154 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.37 (s, 1H, H2), 8.32 (d, *J* = 9.5 Hz, 1H, H8), 8.07 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 9.5 Hz, 1H, H7). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 146.5, 138.9, 134.0, 131.8, 128.2, 128.1, 127.0, 126.8, 121.2, 118.9. Elemental analysis: calcd (%) for $C_{12}H_7BrClN_3$ (308.56): C 46.71, H 2.29; found: C 46.78, H 2.35.

Methyl 2-(6-chloroimidazo[1,2-*b*]pyridazin-3-yl)benzoate (33): Following the general procedure using methyl 2-bromobenzoate (0.215 g, 1 mmol) and 6-chloroimidazo[1,2-*b*]pyridazine (0.169 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 55:45) to afford the desired compound **33** (0.170 g, 59%) as a yellow solid (mp = 144-147 ºC). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 8.29 (d, *J* = 9.5 Hz, 1H, H8), 8.07 (s, 1H, H2), 7.96 (dd, *J* = 1.5 and 7.7 Hz, 1H), 7.75 (ddd, *J* = 1.5, 7.4 and 7.5 Hz, 1H), 7.68-7.60 (m, 2H), 7.40 (d, *J* = 9.5 Hz, 1H, H7), 3.57 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 167.1, 145.8, 137.9, 133.7, 132.3, 131.8, 130.4, 129.9, 129.2, 128.4,

128.0, 126.8, 118.7, 52.1. Elemental analysis: calcd (%) for C$_{14}$H$_{10}$ClN$_3$O$_2$ (287.70): C 58.45, H 3.50; found: C 58.76, H 3.41.

6-Chloro-3-(naphthalen-1-yl)imidazo[1,2-*b*]pyridazine (34): Following the general procedure using 1-bromonaphthalene (0.207g, 1 mmol) and 6-chloroimidazo[1,2-*b*]pyridazine (0.169 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 45:55) to afford the desired compound **34** (0.213 g, 76%) as a white solid (mp = 180-183 ºC). ^{1}H NMR (400 MHz, *d$_6$*-DMSO) δ (ppm) 8.36 (d, *J* = 9.5 Hz, 1H, H7), 8.12 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 1H, H2), 8.07 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 1.5 and 7.0 Hz, 1H), 7.68 (dd, *J* = 7.3 and 8.2 Hz, 1H), 7.62-7.55 (m, 2H), 7.5 (ddd, *J* = 1.6, 6.6 and 8.6 Hz, 1H), 7.43 (d, *J* = 9.5 Hz, 1H, H8). ^{13}C NMR (100 MHz, *d$_6$*-DMSO) δ (ppm) 146.4, 138.0, 135.0, 133.3, 129.6, 129.1, 128.5, 128.1, 126.9, 126.3, 125.5, 126.3, 125.5, 125.2, 124.9, 119.0. Elemental analysis: calcd (%) for C$_{16}$H$_{10}$ClN$_3$ (279.73): C 68.70, H 3.60; found: C 69.12, H 3.98.

3-(6-Chloroimidazo[1,2-*b*]pyridazin-3-yl)quinoline (35): Following the general procedure using 3-bromoquinoline (0.208 g, 1 mmol) and 6-chloroimidazo[1,2-*b*]pyridazine (0.169 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 20:80) to afford the desired compound **35** (0.174 g, 62%) as a yellow solid (mp = 218-221 ºC). ^{1}H NMR (400 MHz, *d$_6$*-DMSO) δ (ppm) 9.55 (d, *J* = 2.3 Hz, 1H), 9.08 (d, *J* = 2.3 Hz, 1H), 8.59 (s, 1H), 8.38 (d, *J* = 9.5 Hz, 1H, H7), 8.11-8.06 (m, 2H), 7.82 (ddd, *J* = 1.5, 6.9 and 8.5 Hz, 1H), 7.69 (dd, *J* = 6.9 and 8.2 Hz, 1H), 7.52 (d, *J* = 9.5 Hz, 1H, H8). ^{13}C NMR (100 MHz, *d$_6$*-DMSO) δ (ppm) 148.7, 146.7, 146.6, 129.2, 134.5, 131.8, 130.0, 128.8, 128.5, 128.3, 127.4, 127.2, 125.3, 121.4, 119.4. Elemental analysis: calcd (%) for C$_{15}$H$_9$ClN$_4$ (280.72): C 64.18, H 3.23; found: C 64.28, H 3.45.

6-Chloro-3-(pyridin-3-yl)imidazo[1,2-*b*]pyridazine (36): Following the general procedure using 3-bromopyridine (0.157 g, 1 mmol) and 6-chloroimidazo[1,2-*b*]pyridazine (0.169 g, 1.1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 60:40) to afford the desired compound **36** (0.134 g, 58%) as a yellow solid (mp = 144-147 ºC). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 9.23 (d, *J* = 2.0 Hz, 1H), 8.63 (dd, *J* = 1.5 and 4.8 Hz, 1H), 8.42 (td, *J* = 1.9 and 8.0 Hz, 1H), 8.01 (s, 1H), 7.99 (d, *J* = 9.4 Hz, 1H), 7.46-7.43 (m, 1H), 7.14 (d, *J* = 9.4 Hz, 1H). This is a known compound and the spectral data are identical to those reported in literature.[11]

2-Bromo-3-(4-fluorophenyl)imidazo[1,2-*b*]pyridazine (37): 3-(4-Fluorophenyl)imidazo[1,2-*b*]pyridazine (**8**) (0.213, 1 mmol), *N*-bromosuccinimide (0.196 g, 1.1 mmol) were heated in 5 mL chloroform at reflux for 12 hour. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (pentane-Et$_2$O, 45:55) to afford the desired compound **37** (0.278 g, 95%) as a white solid (mp = 172-173 ºC). ^{1}H NMR (400 MHz, *d$_6$*-DMSO) δ (ppm) 8.57 (dd, *J* = 1.6 and 4.6 Hz, 1H, H6), 8.17 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 7.82 (dd, *J* = 5.4 and 8.4 Hz, 2H), 7.41 (t, *J* = 8.9 Hz, 2H), 7.35 (dd, *J* = 4.6 and 9.2 Hz, 1H, H7). ^{13}C NMR (100 MHz, *d$_6$*-DMSO) δ (ppm) 162.0 (d, *J* = 247.1 Hz), 144.2, 138.2, 131.8 (d, *J* = 8.1 Hz), 125.0, 124.1, 123.0, 121.8, 118.7, 115.5 (d, *J* = 21.4 Hz). Elemental analysis: calcd (%) for C$_{12}$H$_7$BrFN$_3$ (292.11): C 49.34, H 2.42; found: C 49.57, H 2.56.

3-(4-Fluorophenyl)-2-phenylimidazo[1,2-*b*]pyridazine (38): The reaction of 2-bromo-3-(4-fluorophenyl)imidazo[1,2-*b*]pyridazine (**37**) (0.146 g, 0.5 mmol), phenylboronic acid (0.073 g, 0.6 mmol) and K$_3$PO$_4$ (0.212 g, 1 mmol) at 80 °C over 15 h in 1,4-dioxane (1 mL) in the presence of PdCl(C$_3$H$_5$)(dppb) (6 mg, 0.01 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **38** (0.124 g, 86%) as a pale yellow solid (mp = 126-129 ºC). ^{1}H NMR (400 MHz, *d$_6$*-DMSO) δ (ppm) 8.49 (dd, *J* = 1.7 and 4.4 Hz, 1H, H6), 8.2 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 7.64-7.58 (m, 4H), 7.39-7.26 (m, 6H). ^{13}C NMR (100 MHz, *d$_6$*-DMSO) δ (ppm) 162.2 (d, *J* = 245.3 Hz), 143.7, 141.8, 138.3, 133.8, 132.9 (d, *J* = 8.4 Hz), 128.5, 127.9, 127.7, 125.3, 125.1 (m), 123.4, 118.1, 115.9 (d, *J* = 22.3 Hz).

Elemental analysis: calcd (%) for C$_{18}$H$_{12}$FN$_3$ (289.31): C 74.73, H 4.18; found: C 74.89, H 4.07.

3-(4-fluorophenyl)-2-(thiophen-3-yl)imidazo[1,2-*b*]pyridazine (39): The reaction of 2-bromo-3-(4-fluorophenyl)imidazo[1,2-*b*]pyridazine (**37**) (0.146 g, 0.5 mmol), thiophen-3-ylboronic acid (0.077 g, 0.6 mmol) and K$_3$PO$_4$ (0.212 g, 1 mmol) at 80 °C over 15 h in 1,4-dioxane (1 mL) in the presence of PdCl(C$_3$H$_5$)(dppb) (6 mg, 0.01 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **39** (0.131 g, 89%) as a white solid (mp = 186-189 ºC). ^{1}H NMR (400 MHz, *d$_6$*-DMSO) δ (ppm) 8.46 (dd, *J* = 1.6 and 4.4 Hz, 1H, H6), 8.17 (dd, *J* = 1.6 and 9.2 Hz, 1H, H8), 7.65-7.60 (m, 2H), 7.55 (dd, *J* = 3.1 and 5.1 Hz, 1H), 7.4 (t, *J* = 8.8 Hz, 2H), 7.28 (dd, *J* = 4.4 and 9.2 Hz, 2H), 7.21 (dd, *J* = 1.0 and 5.1 Hz, 1H). ^{13}C NMR (100 MHz, *d$_6$*-DMSO) δ (ppm) 162.3 (d, *J* = 248.3 Hz), 143.6, 138.3, 138.1, 135.1, 133.0 (d, *J* = 9.5 Hz), 126.5, 126.4, 125.0, 124.9 (m), 123.2, 122.9, 118.0, 115.9 (d, *J* = 21.7 Hz). Elemental analysis: calcd (%) for C$_{16}$H$_{10}$FN$_3$S (295.34): C 65.07, H 3.41; found: C 65.28, H 3.56.

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Phosphine-free Pd(OAc)$_2$–catalyzed direct arylation of imidazo[1,2-b]pyridazines at C3 position under very low catalyst concentration in eco-friendly solvents. Both aryl bromides and aryl chlorides have been used as coupling partners. TOFs up to 10000 h^{-1} have been obtained.
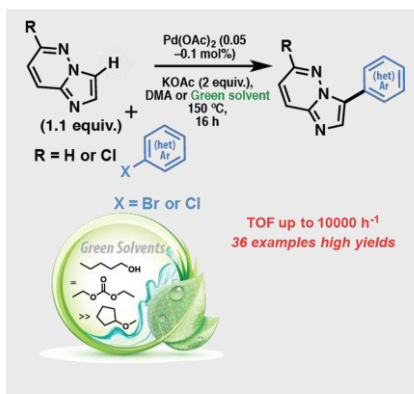
S. Chikhi, S. Djebbar,] J.-F. Soulé,[a] and H. Doucet**

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Environmentally-Safe Conditions for the Palladium-Catalyzed Direct C3-Arylation with High Turn Over Frequency of Imidazo[1,2-b]pyridazines Using Aryl Bromides and Chlorides