DOI: 10.1002/ejoc.200900849

Direct Arylation of Imidazo[1,2-*b*]pyridazines: Microwave-Assisted One-Pot Suzuki Coupling/Pd-Catalysed Arylation

Ahmed El Akkaoui,[a,b] Sabine Berteina-Raboin,*[a] Abderrahim Mouaddib,[b] and Gérald Guillaumet[a]

Keywords: Imidazo[1,2-*b*]pyridazines / C–H arylation / Microwaves / Multicomponent reactions / Cross-coupling / C–C coupling

Direct intermolecular C–H arylation of 6-chloroimidazo[1,2-*b*]-pyridazine in its 3-position was achieved, and the tolerance to reaction conditions in the presence of chloro groups was investigated. Various 3-(hetero)arylimidazo[1,2-*b*]pyridazines were synthesized in good to excellent yields. This methodology was successfully applied to the synthesis of 3,6-di- and 2,3,6-trisubstituted imidazo[1,2-*b*]pyridazines by a microwave-assisted, one-pot, two-step Suzuki cross-coupling/palladium-catalysed arylation process.

Introduction

Direct transition-metal-catalysed reactions for the elaboration of C–C_{Ar} bonds are widely used in organic synthesis,[1] and the development of powerful catalytic methods has opened new routes to the synthesis of complex molecules. Usually, heteroaryl–aryl bonds are generated by coupling of two functionalized heteroaromatic carbon atoms, but that is not always necessary. It is sometimes possible to introduce an aryl group directly onto an aromatic ring by replacing a C–H bond with a C–C bond. In the past three decades, development of transition-metal-catalysed C–H activation reactions has received considerable attention, and a wide range of metal catalysts, including Pd,[2] Ru[3] and Rh[4] catalysts, have been exploited with varying levels of success.

As a continuation of the research into imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*]pyridazine derivatives carried out in our laboratories,[5] our group has investigated the use of direct arylation to functionalize imidazo[1,2-*a*]pyridine at its 3-position by use of aryl bromides or heteroaryl bromides.[6] Here we report the details of our studies of the functionalization of imidazo[1,2-*b*]pyridazines with aryl bromides. In addition, we demonstrate that various functionalities can be introduced by subsequent palladium-catalysed cross-coupling reactions or aromatic substitutions from imidazo[1,2-*b*]pyridazines halogenated at the 6-position to obtain 2,3,6-trisubstituted imidazo[1,2-*b*]pyridazine derivatives.

As far as we know, there is no standard methodology described in the literature for the synthesis of such compounds.

We have also shown that this procedure can be applied to quick syntheses of polysubstituted imidazo[1,2-*b*]pyridazines by a microwave-assisted, one-pot, two-step Suzuki cross-coupling/palladium-catalysed arylation process.

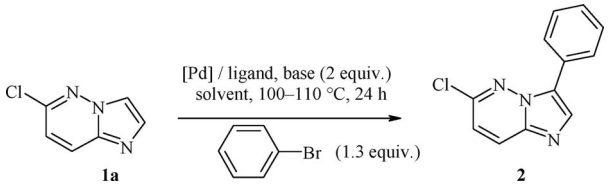
Results and Discussion

As a model, we began with the investigation of the direct cross-coupling arylation reaction between bromobenzene and 6-chloroimidazo[1,2-*b*]pyridazine (**1a**).[7] We first tested reaction conditions already used in our laboratory for the (hetero)arylation of imidazo[1,2-*a*]pyridine by use of palladium(II) acetate (5 mol-%), triphenylphosphane (10 mol-%), K_2CO_3 (2 equiv.) and dioxane at 100 °C[6] (Table 1). Treatment of 6-chloroimidazo[1,2-*b*]pyridazine (**1a**) under these reaction conditions for 24 h thus gave **2**, but in only 50% yield (Table 1, Entry 1), with a significant amount of starting material being recovered.

Increasing the amounts of palladium(II) acetate to 10 mol-% and triphenylphosphane to 20 mol-% under the same reaction conditions led to compound **2** in 91% yield (Table 1, Entry 2). The use of DMA as solvent lowered the yield to 76% (Table 1, Entry 3). The best conditions were found with toluene as solvent: compound **2** was then obtained in 93% yield with 100% conversion (Table 1, Entry 4). Other ligands such as $AsPh_3$, $(o\text{-tolyl})_3P$ and Xantphos (Table 1, Entries 5–7) were also tested. A change in the base afforded product **2** in 80% yield (Table 1, En-

[a] Institut de Chimie Organique et Analytique, Université d'Orléans, UMR CNRS 6005,
B. P. 6759, 45067 Orléans Cedex 2, France
Fax: +33-2-38417281
E-mail: sabine.berteina-raboin@univ-orleans.fr
[b] Laboratoire de Chimie Bio-Organique et Analytique, F.S.T. B-M, Université Sultan Moulay Slimane,
B. P. 523, 23000 Beni-Mellal, Morocco

Table 1. Optimization of the reaction conditions for the arylation of **1a** with bromobenzene.



1a **2**

Entry	Catalyst	Base	Solvent	Conversion (%)	Yield (%)[a]
1	5% $Pd(OAc)_2$/10% PPh_3	K_2CO_3	dioxane	64	50
2	10% $Pd(OAc)_2$/20% PPh_3	K_2CO_3	dioxane	100	91
3	10% $Pd(OAc)_2$/20% PPh_3	K_2CO_3	DMA	85	76
4	**10% $Pd(OAc)_2$/20% PPh_3**	**K_2CO_3**	**toluene**	**100**	**93**
5	10% $Pd(OAc)_2$/20% $AsPh_3$	K_2CO_3	toluene	92	87
6	10% $Pd(OAc)_2$/20% P(*o*-tolyl)$_3$	K_2CO_3	toluene	98	92
7	10% $Pd(OAc)_2$/20% Xantphos	K_2CO_3	toluene	90	86
8	10% $Pd(OAc)_2$/20% PPh_3	Cs_2CO_3	toluene	88	80
9	10% $Pd(OAc)_2$/20% PPh_3	Na_2CO_3	toluene	17	10
10	10% $Pd(PPh_3)_4$	K_2CO_3	toluene	95	88
11	10% $PdCl_2(PPh_3)_2$	K_2CO_3	toluene	20	13

[a] Yields given are for isolated compound **2**.

try 8) with caesium carbonate or in 10% yield (Table 1, Entry 9) with sodium carbonate. We next focused our attention on the influence of the catalyst system on the cross-coupling arylation reaction. The use of $Pd(PPh_3)_4$ instead of $Pd(OAc)_2/PPh_3$ gave compound **2** in 88% yield (Table 1, Entry 10). In contrast, $Pd(PPh_3)_2Cl_2$ afforded compound **2** in poor yield, and starting material was recovered (Table 1, Entry 11).

Finally, we found that the optimum reaction conditions were 6-chloroimidazo[1,2-*b*]pyridazine (**1a**, 1 equiv.), bromobenzene (1.3 equiv.), palladium(II) acetate (10 mol-%), triphenylphosphane (20 mol-%) and K_2CO_3 (2 equiv.) in toluene at 110 °C (Table 1).

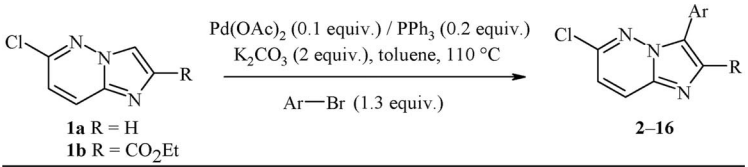
The efficiency of the $Pd(OAc)_2/PPh_3$ catalyst system for C-3 arylation of 6-chloroimidazo[1,2-*b*]pyridazines with deactivated bromobenzene was confirmed. The scope of this reaction under the optimized conditions (Table 1, Entry 4) was next investigated with several aryl bromides. The results (Table 2) showed that compound **1a** could be efficiently functionalized at its 3-position. Under the same reaction conditions, ethyl 6-chloroimidazo[1,2-*b*]pyridazine-2-carboxylate (**1b**) was also arylated in good yield (Table 2, Entry 2). It is noteworthy that this reaction can be applied to a wide variety of aryl bromides. Both electron-rich (R = Me, OMe) and electron-poor (R = Cl, CN, CO_2Me, NO_2) haloaromatics reacted to give good to excellent yields (78–98%). Some heterocyclic bromides were also used for direct arylation, which led to pyridylimidazo[1,2-*b*]pyridazines derivatives **14**–**16** in good yields (75–95%, Table 2, Entries 13–15).

Our next intent was to determine the effect on our arylation procedure of substitution at the 2-positions of imidazo[1,2-*b*]pyridazines. To that end we investigated different combinations of 2-arylimidazo[1,2-*b*]pyridazines **1a**–**g**, obtained by standard procedures,[8] with various aryl bromides (Table 3). We had previously demonstrated the favourable influence of microwave irradiation for the preparation of functionalized 2-substituted imidazo[1,2-*a*]pyridines. We decided to apply this technique[9] to a reaction mixture consisting of 6-chloroimidazo[1,2-*b*]pyridazine (**1a**) and 1-bromo-4-nitrobenzene, which was irradiated under the conditions previously optimized with conventional heating [$Pd(OAc)_2$ (10 mol-%), PPh_3 (20 mol-%)]. Under these conditions, at 140 °C for 2 h, compounds **2** and **3** were isolated in 93% and 96% yields, respectively (Table 3, Entries 1 and 2).

The presence of aryl groups in the 2-positions of 6-chloroimidazo[1,2-*b*]pyridazines **1c**–**g** lowered the yields to 75–85% (Table 3, Entries 3–7), probably because of steric hindrance.

The halogen substitution on the arylated imidazo[1,2-*b*]-pyridazines allowed simple functionalization of the heterocycle through metal-catalysed coupling reactions or aromatic substitutions. Aryl substituents, for example, were introduced at the 6-position in imidazo[1,2-*b*]pyridazine **1a** through Suzuki cross-coupling. On the other hand, the reaction between starting material **1a** and *p*-methoxyphenylboronic acid under the same optimized conditions led to incomplete conversion (10% of starting material **1a** was recovered), and the desired compound **22** (Scheme 2, below) was obtained in only 78% yield (Table 4, Entry 1). However, complete conversion could be achieved in only 3 h when the reaction mixture was heated at reflux in a toluene/ethanol mixture (2:1), leading to the desired compound **22** in 98% yield. With these results to hand, we speculated that this methodology might be extendable to the synthesis of various 3,6-disubstituted imidazo[1,2-*b*]pyridazine analogues. The starting materials **1a** and **8** were thus treated with various arylboronic acids under the optimized conditions [80 °C, toluene/ethanol (2:1), 3 h], to provide products **23** and **24** in excellent yields (Table 4, Entries 3 and 4). We then decided to try S_NAr and palladium-catalysed *N*-arylation reactions. Compound **7** was treated with sodium methoxide, affording product **25** in 95% yield (Table 4, En-

Table 2. Arylation and heteroarylation of 6-chloroimidazo[1,2-*b*]pyridazines.



1a R = H
1b R = CO_2Et

2–16

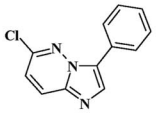
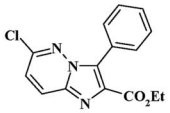
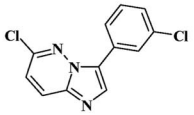
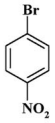
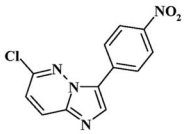
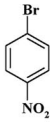
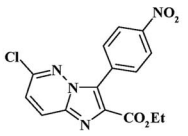
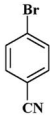
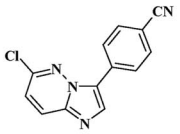
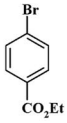
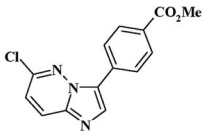
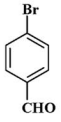
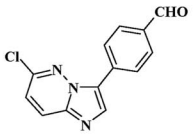
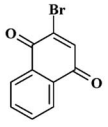
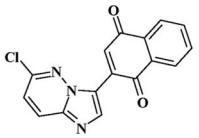
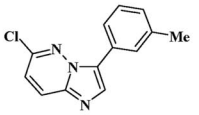
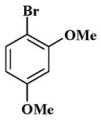
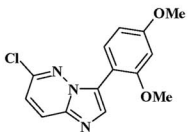
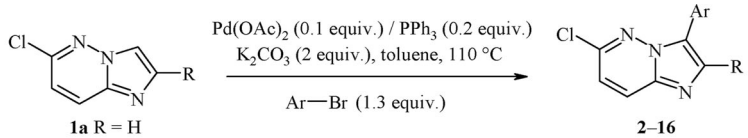
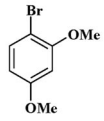
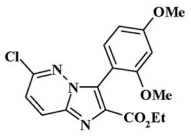
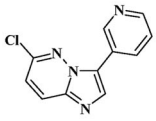
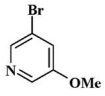
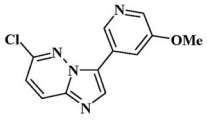
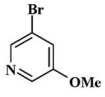
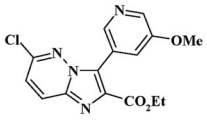
Entry	ArBr	*t* [h]	Product		Yield[a] [%]
1		24		**2**	93
2		8		**3**	91
3		10		**4**	87
4		12		**5**	93
5		8		**6**	97
6		12		**7**	87
7		10		**8**	96
8		10		**9**	98
9		24		**10**	83[b]
10		24		**11**	89
11		24		**12**	78

Table 2. *(Continued.)*



Entry	ArBr	*t* [h]	Product		Yield[a] [%]
12		24		**13**	80
13		24		**14**	95
14		24		**15**	75[b,c]
15		24		**16**	89[b]

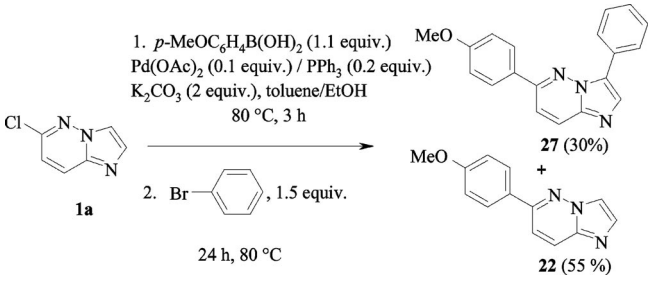
[a] Isolated yield after purification by chromatography. [b] Reaction carried out with 2 equiv. of aryl bromides. [c] 10% of **1a** was recovered.

try 5). Under the palladium-catalysed amination conditions recently developed in our laboratory,[10] in the presence of Xantphos,[11] $Pd(OAc)_2$, K_2CO_3 and *p*-methoxyaniline at reflux in dioxane, product **26** was obtained in 90% yield (Table 4, Entry 6).

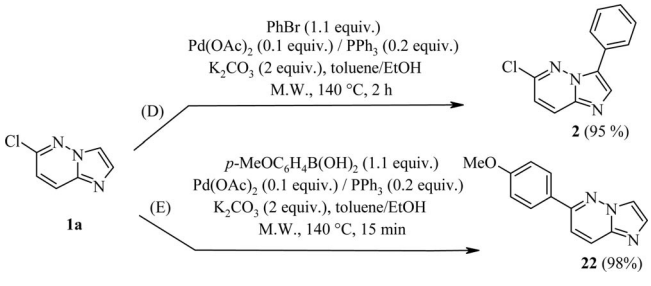
One-Pot Suzuki Coupling/Arylation on 6-Chloroimidazo-[1,2-*b*]pyridazines

We decided to investigate a method based on our previous work[12] for one-pot double Suzuki coupling/arylation of 6-chloroimidazo[1,2-*b*]pyridazines. From our previous results on monosubstitution of the 6-chloroimidazo[1,2-*b*]-pyridazines (Tables 1, 2, and 3), we developed a one-pot Suzuki coupling/direct arylation sequence for successive introduction of distinct (hetero)aryl groups at the 6-position and then in the 3-position. This could provide a very interesting and straightforward route to diversely polysubstituted imidazo[1,2-*b*]pyridazines (Table 5). As far as we know, there have been no reports of one-pot Suzuki coupling/direct arylation of 6-chloroimidazo[1,2-*b*]pyridazines. Initial efforts were directed towards the application of the reaction conditions used successfully for Suzuki cross-coupling and direct arylation (Scheme 1).

Interestingly, although some bis(coupled) product **27** was isolated, the overall yield was quite modest (30%) and the mono(coupled) compound **22** (Suzuki coupling) was obtained in 55% yield (Scheme 1). To overcome these limitations, an alternative strategy was then investigated. This approach is based on the use of microwave irradiation (Scheme 2).

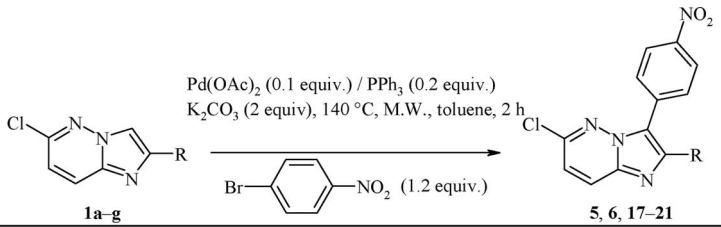


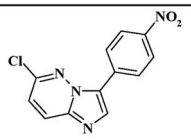
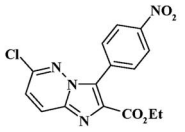
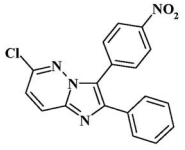
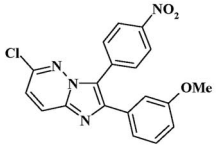
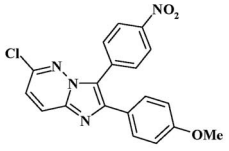
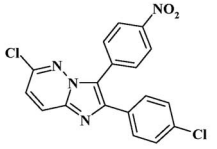
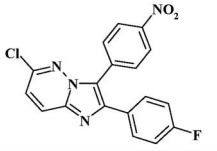
Scheme 1. One-pot Suzuki coupling/arylation on 6-chloroimidazo[1,2-*b*]pyridazine.



Scheme 2. Microwave-assisted Suzuki cross-coupling and arylation with 6-chloroimidazo[1,2-*b*]pyridazine (**1a**).

Table 3. Arylation of 2-substituted imidazo[1,2-*b*]pyridazines with 1-bromo-4-nitrobenzene.



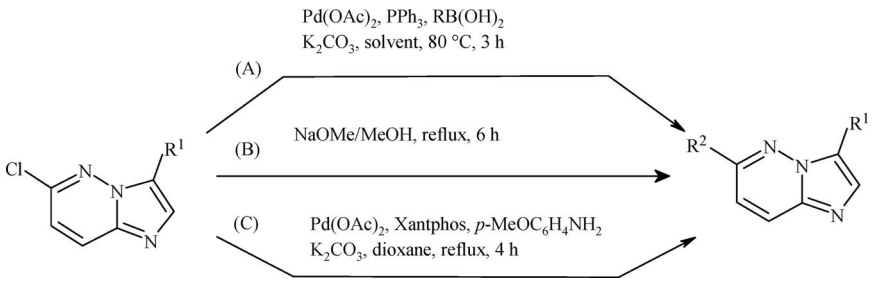
Entry	SM[a]	R	Product		Yield[b] [%]
1	**1a**	H		**5**	93
2	**1b**	CO_2Et		**6**	96
3	**1c**	C_6H_5		**17**	85
4	**1d**	*m*-$MeOC_6H_4$		**18**	75
5	**1e**	*p*-$MeOC_6H_4$		**19**	80
6	**1f**	*p*-ClC_6H_4		**20**	82
7	**1g**	*p*-FC_6H_4		**21**	80

[a] Starting material. [b] Isolated yield after purification by flash chromatography.

Coupling with 6-chloroimidazo[1,2-*b*]pyridazine (**1a**) rapidly afforded either product **2** (regioselective arylation) or product **22** (Suzuki coupling) in excellent yields with use either of regioselective arylation conditions D [$Pd(OAc)_2$/PPh_3 as catalyst in a toluene/EtOH mixture at 140 °C, PhBr (1.5 equiv.), 2 h, M.W., 95%] or of Suzuki coupling conditions E [$Pd(OAc)_2$/PPh_3 as catalyst in a toluene/EtOH mixture at 140 °C, *p*-methoxyphenylboronic acid (1.1 equiv.), 15 min, M.W., 98%], respectively (Scheme 2).

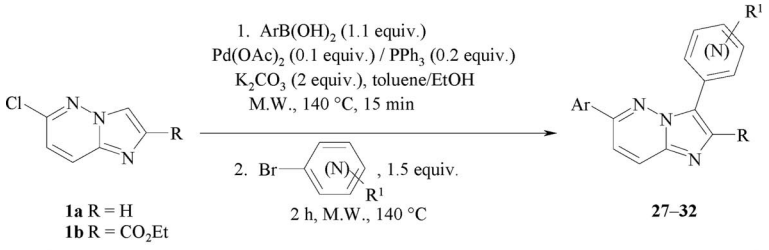
The one-pot cross-coupling between **1a**, *p*-methoxyphenylboronic acid and bromobenzene under the optimized arylation and Suzuki reaction conditions assisted by microwave irradiation [$Pd(OAc)_2$/PPh_3 as catalyst in a toluene/EtOH mixture at 140 °C, M.W.] (Table 5) afforded the expected 3,6-disubstituted imidazo[1,2-*b*]pyridazine **27** in 71% yield without any traces of the monosubstituted product **22** (Suzuki coupling). With a suitable protocol to hand, the scope of the one-pot tandem Suzuki/arylation coupling

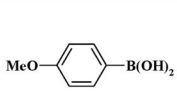
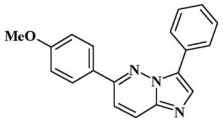
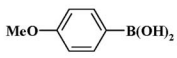
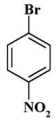
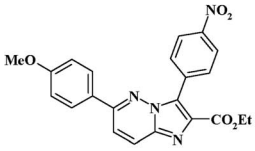
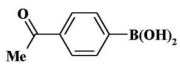
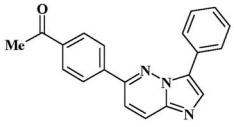
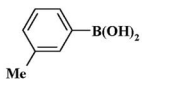
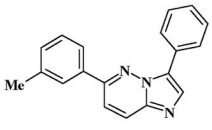
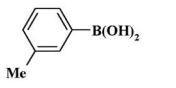
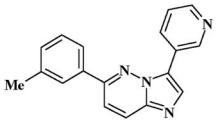
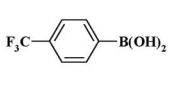
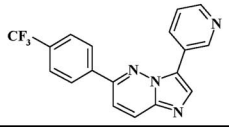
Table 4. Further functionalization of arylated 6-chloroimidazo[1,2-*b*]pyridazines.



Entry	R^1	R^2	Conditions	Product, yield (%)
1	H	*p*-$MeOC_6H_4$	(A), toluene	**22**, 78%
2	H	*p*-$MeOC_6H_4$	(A), toluene/ethanol (2:1)	**22**, 98%
3	3-pyridyl	*m*-NCC_6H_4	(A), toluene/ethanol (2:1)	**23**, 92%
4	*p*-NCC_6H_4	*p*-$F_3CC_6H_4$	(A), toluene/ethanol (2:1)	**24**, 96%
5	*p*-NCC_6H_4	MeO	(B)	**25**, 95%
6	*p*-NCC_6H_4	*p*-$MeOC_6H_4NH$	(C)	**26**, 90%

Table 5. Results of one-pot Suzuki coupling/Pd-catalysed arylation under microwave irradiation conditions.



Entry	$ArB(OH)_2$	ArBr	Product	Yield[a] [%]
1				**27** 72
2				**28** 76
3				**29** 76
4				**30** 69
5				**31** 74
6				**32** 78

[a] Isolated yield (after purification by flash chromatography).

was extended to the synthesis of various polysubstituted imidazo[1,2-*b*]pyridazine analogues. Thus, under microwave irradiation conditions, 6-chloroimidazo[1,2-*b*]pyridazine was treated successively in one-pot fashion without workup with palladium acetate, triphenylphosphane and one of a number of boronic acids (1.1 equiv.), and the reaction mixture was then irradiated for 15 min (Suzuki coupling). After the system had cooled to room temperature, one of a number of aryl bromides (1.5 equiv.) was added, and the reaction mixture was irradiated again for 2 h (direct arylation). These sequences afforded the desired polysubstituted imidazo[1,2-*b*]pyridazines in nearly quantitative conversions. Compounds **27**–**32** were isolated in good overall yields (69–78%, Table 5, Entries 1–6).

Conclusions

We initially developed a short and efficient approach for the Pd^0-mediated arylation of imidazo[1,2-*b*]pyridazines at the C-3 position with aryl bromides. The efficiency and scope of this procedure was established by the synthesis of a library of various 3-substituted and 2,3-disubstituted 6-chloroimidazo[1,2-*b*]pyridazines. We established optimal conditions with the use of the $Pd(OAc)_2/PPh_3$ system as catalyst in toluene at 110 °C. We have also demonstrated that this procedure could be applied to the synthesis of 2,3,6-trisubstituted imidazo[1,2-*b*]pyridazines by a microwave-assisted, one-pot, two-step Suzuki cross-coupling/palladium-catalysed arylation sequence. This approach has the potential to be of great benefit in an easy and convergent synthesis of polysubstituted imidazo[1,2-*b*]pyridazines.

Experimental Section

General Remarks: All reagents were purchased from Sigma–Aldrich, Acros Organics or Alfa Aesar and were used without further purification. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance II 400 spectrometer (^1H: 400 MHz; ^{13}C: 100 MHz) with tetramethylsilane as the internal standard; multiplicities were determined by use of the DEPT 135 sequence. Chemical shifts (δ) are reported in ppm. Coupling constants are reported in Hz. Splitting patterns are designated as s = singlet, d = doublet, t = triplet, m = multiplet. High-resolution mass spectra (HRMS) were recorded with a TOF spectrometer in the electrospray ionization (ESI) mode or with a Finnigan MAT 95 XL spectrometer in the chemical ionization (CI) mode at the Regional Center of Physical Measurement, Blaise Pascal University, Clermont Ferrand. All commercial solvents were used without further purification. Column chromatography was carried out with silica gel 60N (spherical, neutral, 40–63 mm, Merck).

General Procedure for the Palladium-Catalysed C-3 Arylation of 6-Chloroimidazo[1,2-*b*]pyridazine with Aryl and Heteroaryl Bromides: A mixture of 6-chloroimidazo[1,2-*b*]pyridazine (0.1 g, 0.65 mmol), an aryl or heteroaryl bromide (0.85 mmol, 1.3 equiv.), K_2CO_3 (1.3 mmol, 2 equiv.), PPh_3 (0.13 mmol, 0.2 equiv.) and $Pd(OAc)_2$ (0.065 mmol, 0.1 equiv.) in toluene (2 mL) was heated to 110 °C. The reaction mixture was stirred for 24 h, and the mixture was then allowed to cool to room temp. and extracted with CH_2Cl_2 (3×). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether). Products **2**, **4** and **8** are known compounds, which were identified by spectral comparison with literature data. The NMR and elemental analysis data for the other products are as follows.

Ethyl 6-Chloro-3-phenylimidazo[1,2-*b*]pyridazine-2-carboxylate (3): Yield: 178 mg, 91%; yellow solid; m.p. 194 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.39 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 7.15 (d, J = 9.5 Hz, 1 H, 7-H), 7.49–7.57 (m, 3 H, H_{Ar}), 7.62–7.69 (m, 2 H, H_{Ar}), 8.02 (d, J = 9.5 Hz, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 61.5, 121.2, 126.4, 128.2, 128.5, 129.7, 130.9, 133.3, 133.6, 136.9, 148.7, 162.8 ppm. HRMS: calcd. for $C_{15}H_{12}ClN_3O_2$ $[M]^+$ 302.0696; found 302.0711.

6-Chloro-3-(4-nitrophenyl)imidazo[1,2-*b*]pyridazine (5): Yield: 166 mg, 93%; yellow solid; m.p. 216 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 9.4 Hz, 1 H, 7-H), 8.33 (d, J = 9.4 Hz, 1 H, 8-H), 8.36–8.40 (m, 4 H, H_{Ar}), 8.53 (s, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.9, 124.0, 125.7, 126.3, 128.3, 134.1, 135.9, 139.8, 146.1, 146.7 ppm. HRMS: calcd. for $C_{12}H_7ClN_4O_2$ $[M]^+$ 275.0336; found 275.0333.

Ethyl 6-Chloro-3-(4-nitrophenyl)imidazo[1,2-*b*]pyridazine-2-carboxylate (6): Yield: 218 mg, 97%; yellow solid; m.p. 205 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, J = 7.1 Hz, 1 H, CH_2CH_3), 4.42 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 7.24 (d, J = 9.4 Hz, 1 H, 7-H), 7.88–7.90 (m, 1 H, H_{Ar}), 7.90–7.92 (m, 1 H, H_{Ar}), 8.08 (d, J = 9.4 Hz, 1 H, 8-H), 8.37–8.39 (m, 1 H, H_{Ar}), 8.39–8.41 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 61.9, 122.1, 123.3, 128.8, 130.6, 132.1, 132.9, 134.4, 137.4, 148.3, 149.3, 162.5 ppm. HRMS: calcd. for $C_{15}H_{11}ClN_4O_4$ $[M]^+$ 347.0547; found 347.0555.

4-(6-Chloroimidazo[1,2-*b*]pyridazin-3-yl)benzonitrile (7): Yield: 144 mg, 87%; yellow solid; m.p. 214 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 9.4 Hz, 1 H, 7-H), 7.78 (m, 2 H, H_{Ar}), 8.01 (d, J = 9.4 Hz, 1 H, H_{Ar}), 8.17 (s, 1 H, H_{Ar}), 8.21 (m, 2 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.5, 118.8, 119.4, 126.7, 127.2, 127.7, 132.3, 132.7, 134.8, 139.6, 147.4 ppm. HRMS: calcd. for $C_{13}H_7ClN_4$ $[M]^+$ 255.0437; found 255.0435.

4-(6-Chloroimidazo[1,2-*b*]pyridazin-3-yl)benzaldehyde (9): Yield: 164 mg, 98%; yellow solid; m.p. 148 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, J = 9.4 Hz, 1 H, 7-H), 7.94–8.05 (m, 3 H, H_{Ar}), 8.18 (s, 1 H, 2-H), 8.25 (m, 2 H, H_{Ar}, 8-H), 10.05 (s, 1 H, C*H*O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.2, 126.7, 127.6, 130.2, 133.6, 134.9, 135.6, 139.6, 147.3, 191.5 ppm. HRMS: calcd. for $C_{13}H_8ClN_3O$ $[M]^+$ 258.0434; found 258.0428.

6-Chloro-3-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)imidazo[1,2-*b*]pyridazine (10): Yield: 167 mg, 83%; yellow solid; m.p. 235 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, J = 9.4 Hz, 1 H, 7-H), 7.75–7.82 (m, 2 H, H_{Ar}), 8.06 (d, J = 9.4 Hz, 1 H, 8-H), 8.09–8.16 (m, 1 H, H_{Ar}), 8.16–8.22 (m, 1 H, H_{Ar}), 8.37 (s, 1 H, H_{Ar}), 8.88 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.5, 121.1, 126.1, 127.2, 127.6, 131.2, 132.0, 132.5, 133.9, 134.2, 134.5, 140.8, 142.1, 147.5, 183.5, 185.3 ppm. HRMS: calcd. for $C_{16}H_8ClN_3O_2$ $[M]^+$ 310.0383; found 310.0383.

6-Chloro-3-(3-tolyl)imidazo[1,2-*b*]pyridazine (11): Yield: 141 mg, 89%; yellow solid; m.p. 60 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3) 7.01 (d, J = 9.3 Hz, 1 H, 7-H), 7.16–7.18 (m, 1 H, H_{Ar}), 7.36 (dd, J = 9.7, 5.6 Hz, 1 H, H_{Ar}), 7.77 (m, 1 H, H_{Ar}), 7.82 (d, J = 7.8 Hz, 1 H, H_{Ar}), 7.90 (d, J = 9.3 Hz, 1 H, 8-H), 8.01 (s, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 117.9,

123.8, 126.7, 127.1, 127.3, 127.6, 128.6, 129.1, 133.4, 138.3, 138.3, 146.7 ppm. HRMS: calcd. for $C_{13}H_{10}ClN_3$ $[M]^+$ 244.0642; found 244.0631.

6-Chloro-3-(2,4-dimethoxyphenyl)imidazo[1,2-*b*]pyridazine (12): Yield: 147 mg, 78%; yellow solid; m.p. 116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.60–6.62 (m, 2 H, H_{Ar}), 6.66 (dd, J = 8.5, 2.3 Hz, 1 H, H_{Ar}), 7.02 (d, J = 9.3 Hz, 1 H, 7-H, 7-H), 7.86 (d, J = 8.5 Hz, 1 H, H_{Ar}), 7.92 (d, J = 9.3 Hz, 1 H, 8-H), 8.04 (s, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6, 55.7, 99.2, 104.7, 109.6, 117.6, 126.0, 127.0, 130.0, 135.6, 137.7, 146.3, 158.5, 161.4 ppm. HRMS: calcd. for $C_{14}H_{12}ClN_3O_2$ $[M]^+$ 290.0696; found 290.0702.

Ethyl 6-Chloro-3-(2,4-dimethoxyphenyl)imidazo[1,2-*b*]pyridazine-2-carboxylate (13): Yield: 188 mg, 80%; yellow solid; m.p. 155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 3.73 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.36 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 6.60 (d, J = 2.3 Hz, 1 H, H_{Ar}), 6.64 (dd, J = 8.4, 2.3 Hz, 1 H, H_{Ar}), 7.11 (d, J = 9.4 Hz, 1 H, 7-H), 7.37 (d, J = 8.4 Hz, 1 H, H_{Ar}), 7.97 (d, J = 9.4 Hz, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 55.5, 55.6, 61.1, 98.9, 104.7, 108.4, 120.6, 128.2, 130.6, 133.1, 134.3, 136.9, 148.1, 159.1, 162.5, 162.9 ppm. HRMS: calcd. for $C_{17}H_{16}ClN_3O_4$ $[M]^+$ 262.0908; found 262.0919.

6-Chloro-3-(pyridin-3-yl)imidazo[1,2-*b*]pyridazine (14): Yield: 142 mg, 95%; yellow solid; m.p. 145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, J = 9.4 Hz, 1 H, 7-H), 7.43–7.46 (dd, J = 8.0, 3.9 Hz, 1 H, H_{Pyr}), 7.99 (d, J = 9.4 Hz, 1 H, 8-H), 8.01 (s, 1 H, 2-H), 8.42 (td, J = 1.9, 8.0 Hz, 1 H, H_{Pyr}), 8.63 (dd, J = 1.5, 4.8 Hz, 1 H, H_{Pyr}), 9.23 (d, J = 2.0 Hz, 1 H, H_{Pyr}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.0, 121.6, 123.6, 124.3, 126.2, 127.5, 133.6, 139.1, 147.3, 147.8, 149.3 ppm. HRMS: calcd. for $C_{11}H_7ClN_4$ $[M]^+$ 231.0437; found 231.0432.

6-Chloro-3-(5-methoxypyridin-3-yl)imidazo[1,2-*b*]pyridazine (15): Yield: 127 mg, 75%; yellow solid; m.p. 195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, OCH_3), 7.14 (d, J = 9.4 Hz, 1 H, 7-H), 8.01 (d, J = 9.4 Hz, 1 H, 8-H), 8.02–8.04 (m, 1 H, 2-H), 8.15 (s, 1 H, H_{Pyr}), 8.34 (d, J = 2.7 Hz, 1 H, H_{Pyr}), 8.83 (d, J = 1.6 Hz, 1 H, H_{Pyr}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 118.1, 119.0, 124.8, 126.0, 127.6, 133.9, 137.0, 139.2, 140.1, 147.2, 155.6 ppm. HRMS: calcd. for $C_{12}H_9ClN_4O$ $[M]^+$ 261.0543; found 261.0545.

Ethyl 6-Chloro-3-(5-methoxypyridin-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxylate (16): Yield: 192 mg, 89%; yellow solid; m.p. 164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 3.93 (s, 3 H, OCH_3), 4.41 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 7.21 (d, J = 9.5 Hz, 1 H, 7-H), 7.55 (s, 1 H, H_{Ar}), 8.05 (d, J = 9.5 Hz, 1 H, 8-H), 8.40–8.54 (m, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 55.8, 61.6, 121.7, 122.9, 128.6, 129.6, 134.3, 137.3, 138.1, 143.5, 149.0, 162.5 ppm. HRMS: calcd. for $C_{15}H_{13}ClN_4O_4$ $[M]^+$ 333.0754; found 333.0762.

6-Chloro-3-(4-nitrophenyl)-2-phenylimidazo[1,2-*b*]pyridazine (17): Yield: 194 mg, 85%; yellow solid; m.p. 232 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, J = 9.4 Hz, 1 H, 7-H), 7.34–7.40 (m, 3 H, H_{Ar}), 7.57–7.64 (m, 2 H, H_{Ar}), 7.82 (d, J = 8.9 Hz, 1 H, H_{Ar}), 7.99 (d, J = 9.4 Hz, 1 H, 8-H), 8.31 (d, J = 8.9 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.0, 123.4, 124.0, 127.1, 128.8, 128.9, 129.0, 131.0, 133.1, 134.7, 138.2, 145.8, 147.1, 147.5 ppm. HRMS: calcd. for $C_{18}H_{11}ClN_4O_2$ $[M]^+$ 351.0649; found 351.0661.

6-Chloro-2-(3-methoxyphenyl)-3-(4-nitrophenyl)imidazo[1,2-*b*]pyridazine (18): Yield: 186 mg, 75%; yellow solid; m.p. 227 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, OCH_3), 6.92 (dd, J = 8.2, 2.5 Hz, 1 H, H_{Ar}), 7.12 (d, J = 7.6 Hz, 1 H, H_{Ar}), 7.16 (d, J = 9.4 Hz, 1 H, 7-H), 7.19–7.23 (m, 1 H, H_{Ar}), 7.26 (m, 1 H, H_{Ar}), 7.82 (d, J = 8.9 Hz, 2 H, H_{Ar}), 8.00 (d, J = 9.4 Hz, 1 H, 8-H), 8.30 (d, J = 8.9 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 113.9, 115.0, 120.1, 121.2, 123.5, 123.9, 127.1, 129.9, 131.1, 134.3, 134.7, 138.1, 145.6, 147.1, 147.5, 160.0 ppm. HRMS: calcd. for $C_{19}H_{13}ClN_4O_3$ $[M]^+$ 381.0754; found 381.0750.

6-Chloro-2-(4-methoxyphenyl)-3-(4-nitrophenyl)imidazo[1,2-*b*]pyridazine (19): Yield: 198 mg, 80%; yellow solid; m.p. 194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 6.90 (d, J = 8.8 Hz, 2 H, H_{Ar}), 7.15 (d, J = 9.3 Hz, 1 H, 7-H), 7.55 (d, J = 8.8 Hz, 2 H, H_{Ar}), 7.83 (d, J = 8.9 Hz, 2 H, H_{Ar}), 7.97 (d, J = 9.3 Hz, 1 H, 8-H), 8.30 (d, J = 8.9 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 114.3, 119.7, 122.6, 123.9, 125.4, 126.7, 130.0, 130.9, 134.9, 138.1, 145.7, 146.7, 147.4,160.3 ppm. HRMS: calcd. for $C_{19}H_{13}ClN_4O_3$ $[M]^+$ 381.0754; found 381.0771.

6-Chloro-2-(4-chlorophenyl)-3-(4-nitrophenyl)imidazo[1,2-*b*]pyridazine (20): Yield: 205 mg, 82%; yellow solid; m.p. 209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 9.4 Hz, 1 H, 7-H), 7.34 (d, J = 8.5 Hz, 1 H, H_{Ar}), 7.55 (d, J = 8.5 Hz, 1 H, H_{Ar}), 7.80 (d, J = 8.9 Hz, 1 H, H_{Ar}), 7.99 (d, J = 9.4 Hz, 1 H, 8-H), 8.32 (d, J = 8.9 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.3, 123.4, 124.1, 127.1, 129.2, 129.9, 131.0, 131.5, 134.4, 135.1, 138.2, 144.4, 147.3, 147.7 ppm. HRMS: calcd. for $C_{18}H_{10}Cl_2N_4O_2$ $[M + H]^+$ 385.0259; found 385.0271.

6-Chloro-2-(4-fluorophenyl)-3-(4-nitrophenyl)imidazo[1,2-*b*]pyridazine (21): Yield: 192 mg, 80%; yellow solid; m.p. 206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03–7.11 (m, 2 H, H_{Ar}), 7.18 (d, J = 9.4 Hz, 1 H, 7-H), 7.56–7.63 (m, 2 H, H_{Ar}), 7.81 (d, J = 8.9 Hz, 2 H, H_{Ar}), 7.99 (d, J = 9.4 Hz, 1 H, 8-H), 8.31 (d, J = 8.9 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.9, 116.1, 120.2, 123.1, 124.0, 127.0, 129.1, 129.2, 130.5, 130.5, 130.9, 134.5, 138.1, 144.7, 147.1, 147.5,161.9, 164.4 ppm. HRMS: calcd. for $C_{18}H_{10}ClFN_4O_2$ $[M]^+$ 369.0555; found 369.0546.

3-[3-(Pyridin-3-yl)imidazo[1,2-*b*]pyridazin-6-yl]benzonitrile (23): Yield: 178 mg, 92%; yellow solid; m.p. 226 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (ddd, J = 8.0, 4.8, 0.6 Hz, 1 H, H_{Ar}), 7.54 (d, J = 9.5 Hz, 1 H, 7-H), 7.63 (td, J = 7.6, 0.9 Hz, 1 H, H_{Ar}), 7.79 (td, J = 7.7, 1.3 Hz, 1 H, H_{Ar}), 8.15 (d, J = 9.5 Hz, 1 H, 8-H), 8.16 (s, 1 H, 2-H), 8.20–8.28 (m, 2 H, H_{Ar}), 8.37–8.45 (m, 1 H, H_{Pyr}), 8.64 (dd, J = 4.8, 1.5 Hz, 1 H, H_{Pyr}), 9.33 (d, J = 1.6 Hz, 1 H, H_{Pyr}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.7, 115.5, 118.3, 123.7, 124.9, 127.0, 130.2, 130.6, 131.4, 133.5, 133.8, 134.2, 135.3, 136.9, 139.9, 144.6, 147.9, 149.1, 150.0 ppm. HRMS: calcd. for $C_{18}H_{11}N_5$ $[M]^+$ 298.1093; found 298.1102.

4-{6-[4-(Trifluoromethyl)phenyl]imidazo[1,2-*b*]pyridazin-3-yl}benzonitrile (24): Yield: 227 mg, 96%; yellow solid; m.p. 218 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 9.4 Hz, 1 H, 7-H), 7.80 (d, J = 8.4 Hz, 2 H, H_{Ar}), 7.83 (d, J = 8.3 Hz, 2 H, H_{Ar}), 8.12 (d, J = 8.3 Hz, 2 H, H_{Ar}), 8.17 (d, J = 9.4 Hz, 1 H, 8-H), 8.23 (s, 1 H, 2-H), 8.29 (d, J = 8.4 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.1, 116.3, 118.8, 122.5, 125.2, 126.2, 126.3, 126.3, 126.3, 126.6, 126.8, 127.6, 132.1, 132.6, 133.0, 135.2, 138.8, 150.9 ppm. HRMS: calcd. for $C_{20}H_{11}F_3N_4$ $[M]^+$ 365.1014; found 365.1016.

4-(6-Methoxyimidazo[1,2-*b*]pyridazin-3-yl)benzonitrile (25): Yield: 154 mg, 95%; yellow solid; m.p. 186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (s, 3 H, OCH_3), 6.80 (d, J = 9.6 Hz, 1 H, 7-H), 7.74 (d, J = 8.4 Hz, 2 H, H_{Ar}), 7.88 (d, J = 9.6 Hz, 1 H, 8-H), 8.02 (s, 1 H, 2-H), 8.24 (d, J = 8.4 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 54.9, 110.6, 112.4, 118.9, 128.0, 132.0, 132.1, 132.5, 132.9, 133.1, 133.4, 160.1 ppm. HRMS: calcd. for $C_{14}H_{10}N_4O$ $[M + H]^+$ 251.0933; found 251.0925.

4-{6-[(4-Methoxyphenyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}benzonitrile (26): Yield: 200 mg, 90%; yellow solid; m.p. 245 °C. ^1H NMR (400 MHz, DMSO): δ = 3.78 (s, 3 H, OCH_3), 6.99–7.00 (m, 3 H, 7-H, H_{Ar}), 7.61 (d, J = 9.0 Hz, 2 H, H_{Ar}), 7.93 (d, J = 9.7 Hz, 1 H, 8-H), 7.95 (d, J = 8.5 Hz, 2 H, H_{Ar}), 8.11 (s, 1 H, 2-H), 8.35 (d, J = 8.5 Hz, 2 H, H_{Ar}), 9.48 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 55.4, 109.0, 114.0, 114.2, 119.1, 120.8, 125.7, 126.0, 126.4, 132.4, 132.6, 133.2, 133.6, 138.3, 151.2, 154.7 ppm. HRMS: calcd. for $C_{20}H_{15}N_5O$ $[M]^+$ 342.1355; found 342.1371.

General Procedure for the One-Pot Suzuki Coupling/Arylation with 6-Chloroimidazo[1,2-*b*]pyridazines (Table 5): An arylboronic acid (0.72 mmol, 1.1 equiv.), potassium carbonate (1.3 mmol, 2 equiv.), triphenylphosphane (0.13 mmol, 0.2 equiv.), and palladium(II) acetate (0.065 mmol, 0.1 equiv.) were added under argon to a solution of 6-chloroimidazo[1,2-*b*]pyridazine (0.1 g, 0.65 mmol) in a toluene/EtOH mixture [2:1, (v/v), 2 mL] in a microwave tube. The reaction vessel was sealed with a silicon septum and subjected to microwave irradiation at 140 °C with stirring for 15 min. After the mixture had been allowed to cool to room temperature, the aryl or heteroaryl bromide (1.5 equiv.) was injected into the tube by syringe, and the reaction mixture was again subjected to microwave irradiation at 140 °C for 2 h. The reaction vessel was allowed to cool to room temperature, the mixture diluted with dichloromethane (20 mL) and extracted (3 ×). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The crude material thus obtained was purified by column chromatography on silica gel (EtOAc/petroleum ether) to give the polysubstituted imidazo[1,2-*b*]pyridazine derivative (**27**–**32**).

6-(4-Methoxyphenyl)-3-phenylimidazo[1,2-*b*]pyridazine (27): Yield: 141 mg, 72%; yellow solid; m.p. 186 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 7.01 (d, J = 8.7 Hz, 2 H, H_{Ar}), 7.37 (t, J = 7.3 Hz, 1 H, H_{Ar}), 7.44 (d, J = 9.4 Hz, 1 H, 7-H), 7.50–7.51 (m, 2 H, H_{Ar}), 7.93 (d, J = 8.7 Hz, 2 H, H_{Ar}), 7.98 (d, J = 9.4 Hz, 1 H, 8-H), 8.03 (s, 1 H, 2-H), 8.14 (d, J = 7.3 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 114.5, 115.2, 125.8, 126.8, 127.8, 128.2, 128.4, 128.7, 133.0, 139.4, 151.1, 161.2 ppm. HRMS: calcd. for $C_{19}H_{15}N_3O$ $[M]^+$ 302.1293; found 302.1298.

Ethyl 6-(4-Methoxyphenyl)-3-(4-nitrophenyl)imidazo[1,2-*b*]pyridazine-2-carboxylate (28): Yield: 206 mg, 76%; yellow solid; m.p. 192 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 3.87 (s, 3 H, OCH_3), 4.44 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 7.01 (d, J = 8.8 Hz, 2 H, H_{Ar}), 7.66 (d, J = 9.6 Hz, 1 H, 7-H), 7.85 (d, J = 8.8 Hz, 2 H, H_{Ar}), 8.01 (d, J = 8.8 Hz, 2 H, H_{Ar}), 8.10 (d, J = 9.6 Hz, 1 H, 8-H), 8.39 (d, J = 8.8 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 55.5, 61.6, 114.7, 118.7, 123.0, 126.9, 127.1, 128.6, 130.4, 132.1, 133.8, 134.0, 138.2, 147.9, 153.0, 161.9, 162.9 ppm. HRMS: calcd. for $C_{22}H_{18}N_4O_5$ $[M]^+$ 419.1355; found 419.1351.

1-[4-(3-Phenylimidazo[1,2-*b*]pyridazin-6-yl)phenyl]ethanone (29): Yield: 155 mg, 76%; yellow solid; m.p. 162 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.66 (s, 3 H, COCH_3), 7.41 (t, J = 7.4 Hz, 1 H, H_{Ar}), 7.50–7.56 (m, 3 H, H_{Ar}), 8.05–8.11 (m, 6 H, H_{Ar}), 8.13 (d, J = 7.5 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8, 115.1, 126.2, 126.8, 127.2, 128.1, 128.6, 128.8, 128.9, 129.0, 133.7, 137.9, 139.9, 150.2, 197.4 ppm. HRMS: calcd. for $C_{20}H_{15}N_3O$ $[M]^+$ 314.1293; found 314.1299.

3-Phenyl-6-(3-tolyl)imidazo[1,2-*b*]pyridazine (30): Yield: 128 mg, 69%; yellow solid; m.p. 169 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 7.29 (d, J = 7.5 Hz, 1 H, H_{Ar}), 7.35–7.42 (m, 2 H, H_{Ar}), 7.48–7.53 (m, 3 H, H_{Ar}), 7.76–7.79 (m, 2 H, H_{Ar}), 8.03 (d, J = 9.4 Hz, 1 H, 8-H), 8.06 (s, 1 H, 2-H), 8.16 (d, J = 7.4 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 115.7, 124.3, 125.9, 126.9, 127.8, 127.9, 128.7, 128.8, 128.9, 129.0, 130.8, 133.1, 135.8, 138.8, 139.5, 151.7 ppm. HRMS: calcd. for $C_{19}H_{15}N_3$ $[M]^+$ 286.1344; found 286.1354.

3-(Pyridin-3-yl)-6-(3-tolyl)imidazo[1,2-*b*]pyridazine (31): Yield: 138 mg, 74%; yellow solid; m.p. 167 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 7.32 (d, J = 7.5 Hz, 1 H, H_{Ar}), 7.42 (d, J = 7.4 Hz, 1 H, H_{Ar}), 7.45 (dd, J = 7.9, 4.7 Hz, 1 H, H_{Ar}), 7.55 (d, J = 9.5 Hz, 1 H, 8-H), 7.75–7.81 (m, 2 H, H_{Ar}), 8.06 (d, J = 9.5 Hz, 1 H, 8-H), 8.11 (s, 1 H, 2-H), 8.48 (td, J = 8.0, 1.8 Hz, 1 H, H_{Pyr}), 8.62 (dd, J = 4.7, 1.4 Hz, 1 H, H_{Pyr}), 9.40 (d, J = 1.9 Hz, 1 H, H_{Pyr}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 116.5, 123.6, 124.4, 125.3, 125.8, 126.1, 127.8, 129.1, 131.1, 133.3, 133.7, 135.4, 138.9, 139.9, 147.7, 148.6, 152.2 ppm. HRMS: calcd. for $C_{18}H_{14}N_4$ $[M]^+$ 287.1297; found 287.1303.

3-(Pyridin-3-yl)-6-[4-(trifluoromethyl)phenyl]imidazo[1,2-*b*]pyridazine (32): Yield: 172 mg, 78%; yellow solid; m.p. 115 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47 (dd, J = 7.7, 4.8 Hz, 1 H, H_{Ar}), 7.59 (d, J = 9.4 Hz, 1 H, 7-H), 7.80 (d, J = 8.2 Hz, 2 H, H_{Ar}), 8.12 (d, J = 8.1 Hz, 2 H, H_{Ar}), 8.15 (d, J = 9.4 Hz, 1 H, 8-H), 8.18 (s, 1 H, 2-H), 8.45 (td, J = 8.0, 1.5 Hz, 1 H, H_{Pyr}), 8.66 (m, 1 H, H_{Pyr}), 9.40 (m, 1 H, H_{Pyr}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.9, 122.5, 123.7, 123.7, 125.3, 126.1, 126.2, 126.2, 126.2, 126.7, 127.5, 133.7, 134.0, 138.8, 147.7, 148.9, 150.7 ppm. HRMS: calcd. for $C_{18}H_{11}F_3N_4$ $[M]^+$ 341.1014; found 341.1007.

[1] For recent reviews on direct arylation, see: a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; b) L. C. Campeau, D. Stuart, K. Fagnou, *Aldrichim. Acta* **2007**, *40*, 35–41; c) L. C. Campeau, K. Fagnou, *Chem. Commun.* **2006**, 1253–1264; d) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200–205; e) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; f) B. J. Li, S. D. Yang, Z. J. Shi, *Synlett* **2008**, 949–957; g) O. Daugulis, V. G. Zaitsev, D. Shabashov, Q. N. Pham, A. Lazareva, *Synlett* **2006**, 3382–3388; h) S. Pascual, P. De Mendoza, A. M. Echavarren, *Org. Biomol. Chem.* **2007**, *5*, 2727–2734; i) M. Catellani, E. Motti, N. Della Ca', R. Ferraccioli, *Eur. J. Org. Chem.* **2007**, 4153–4165; j) J. C. Lewis, R. C. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025.

[2] For recent examples of direct arylation processes with Pd^0, see: a) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; b) L. Ackermann, A. Althammer, *Angew. Chem. Int. Ed.* **2007**, *46*, 1627–1629; c) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174; d) B. Laleu, M. Lautens, *J. Org. Chem.* **2008**, *73*, 9164–9167; e) L. Ackermann, R. Vicente, R. Born, *Adv. Synth. Catal.* **2008**, *350*, 741–748; f) S. H. Hwang, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 16158–16159; g) F. Bellina, F. Benelli, R. Rossi, *J. Org. Chem.* **2008**, *73*, 5529–5535; h) E. F. Flegeau, M. E. Popkin, M. F. Greaney, *Org. Lett.* **2008**, *10*, 2717–2720; i) T. Martin, C. Verrier, C. Hoarau, F. Marsais, *Org. Lett.* **2008**, *10*, 2909–2912; j) X. Wang, D. V. Gribkov, D. Sames, *J. Org. Chem.* **2007**, *72*, 1476–1479; k) D. H. Wang, T. S. Mei, J. Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 17676–17677; l) J. X. Wang, J. A. McCubbin, M. Jin, R. S. Laufer, Y. Mao, A. P. Crew, M. J. Mulvihilland, V. Snieckus, *Org. Lett.* **2008**, *10*, 2923–2926; m) S. D. Yang, C. L. Sun, Z. Fang, B. J. Li, Y. Z. Li, Z. J. Shi, *Angew. Chem. Int. Ed.* **2008**, *47*, 1473–1476; n) L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem. Int. Ed.* **2009**, *48*, 201–204; o) J. Kim, M. Jo, W. So, Z. No, *Tetrahedron Lett.* **2009**, *50*, 1229–1235; p) P. Li, Z. Chai, G. Zhao, S. Zhu, *Tetrahedron*

2009, *65*, 1673–1678; q) B. Mariampillai, J. Alliot, M. Li, M. Lautens, *J. Am. Chem. Soc.* **2007**, *129*, 15372–15379.

[3] For selected direct arylation processes with Ru, see: a) L. Ackermann, A. Althammer, R. Born, *Angew. Chem. Int. Ed.* **2006**, *45*, 2619–2622; b) I. Ozdemir, S. Demir, B. Cetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H. Dixneuf, *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157.

[4] For selected direct arylation processes with Rh, see: a) S. Oi, S. Fukita, Y. Inoue, *Chem. Commun.* **1998**, 2439–2440; b) R. B. Bedford, S. J. Coles, M. B. Hursthouse, M. E. Limmert, *Angew. Chem. Int. Ed.* **2003**, *42*, 112–114; c) R. B. Bedford, M. E. Limmert, *J. Org. Chem.* **2003**, *68*, 8669–8682; d) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996–4997; e) S. Proch, R. Kempe, *Angew. Chem. Int. Ed.* **2007**, *46*, 3135–3138; f) R. B. Bedford, M. Betham, A. J. M. Caffyn, J. P. H. Charmant, L. C. L. Alleyne, P. D. Long, D. P. Ceron, S. Prashar, *Chem. Commun.* **2008**, 990–992; g) J. C. Lewis, A. M. Berman, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 2493–2500; h) J. C. Lewis, J. Y. Wu, J. A. Ellman, R. G. Bergman, *Angew. Chem. Int. Ed.* **2006**, *45*, 1589–1591; i) J. C. Lewis, S. H. Wiedemann, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2004**, *6*, 35–38; j) K. L. Tan, A. Vasudevan, R. G. Bergman, J. A. Ellman, A. J. Souers, *Org. Lett.* **2003**, *5*, 2131–2134; k) K. L. Tan, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2002**, *124*, 3202–3203; l) S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *Tetrahedron* **2008**, *64*, 6073–6081.

[5] a) G. Guillaumet, S. Berteina-Raboin, S. El Kazzouli, P. Delagrange, D. H. Caignard, WO **2006**,027,474, **2006**; *Chem. Abstr.* **2006**, *144*, 254132; b) S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib, G. Guillaumet, *Tetrahedron Lett.* **2003**, *44*, 6265–6267; c) S. El Kazzouli, A. Berthault, S. Berteina-Raboin, A. Mouaddib, G. Guillaumet, *Lett. Org. Chem.* **2005**, *2*, 184–187; d) A. El Akkaoui, J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib, G. Guillaumet, *Tetrahedron Lett.* **2008**, *49*, 2472–2475; e) J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib, G. Guillaumet, *Synthesis* **2008**, 2537–2542; f) J. Koubachi, S. Berteina-Raboin, A. Mouaddib, G. Guillaumet, *Synthesis* **2009**, *2*, 271–276.

[6] J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib, G. Guillaumet, *Synlett* **2006**, 3237–3242.

[7] a) B. Stanovnik, M. Tisler, *Tetrahedron* **1967**, *23*, 2739–2746; b) B. Stanovnik, M. Tisler, *Tetrahedron* **1967**, *23*, 387–395; c) E. Abignente, F. Arena, P. De Capriis, L. Parente, *Farmaco, Ed. Sci.* **1977**, *32*, 430–437.

[8] A. M. Roe, *J. Chem. Soc.* **1963**, 2195–2200.

[9] a) A. Hallberg, *Tetrahedron Lett.* **1996**, *37*, 8219–8220; b) A. Hallberg, *J. Org. Chem.* **1996**, *61*, 9582–9584; c) P. Nilsson, *Top. Curr. Chem.* **2006**, *266*, 103–144; d) C. O. Kappe, *Chem. Soc. Rev.* **2008**, *37*, 1127–1140.

[10] a) S. El Kazzouli, G. Lavecchia, S. Berteina-Raboin, A. Mouaddib, G. Guillaumet, *Tetrahedron Lett.* **2006**, *47*, 4437–4440; b) E. Garnier, J. Audoux, E. Pasquinet, F. Suzenet, D. Poullain, B. Lebret, G. Guillaumet, *J. Org. Chem.* **2004**, *69*, 7809–7815.

[11] Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene.

[12] J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib, G. Guillaumet, *J. Org. Chem.* **2007**, *72*, 7650–7655.

Received: July 27, 2009
Published Online: January 5, 2010

