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Efficient and highly regioselective direct C-2 arylation of azoles, including free (NH)-imidazole, -benzimidazole and -indole, with aryl halides

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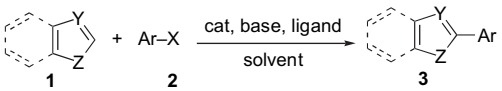
Abstract—The Pd- and Cu-mediated reaction of a large variety of π-electron sufficient heteroarenes, which include free (NH)-imidazoles, -benzimidazole and -indole, with aryl iodides under ligandless and base-free conditions provides regioselectively the required 2-arylheterocycle derivatives in high yields. 2-Aryl-1-phenyl-1*H*-imidazoles can also be prepared by a one-pot domino HALEX and Pd- and Cu-mediated arylation reactions of 1-phenyl-1*H*-imidazole with activated and unactivated aryl bromides under base-free and ligandless conditions. The protocol for the synthesis of 2-arylazoles involving the use of aryl iodides has been found to be suitable for the efficient preparation of three bioactive compounds and a key intermediate in the synthesis of a heparanase inhibitor.

1. Introduction

2-Arylazoles represent privileged structural motifs frequently found in molecules that elicit important biological responses. In fact, 2-aryl-1*H*-indole derivatives include antiprotozoal agents,[1] gonadotropin releasing hormone antagonists,[2] anti-estrogens,[3] h5-HT_{2A} receptor antagonists[4] and compounds that exhibit anti-inflammatory[5] or cytotoxic activity.[6] On the other hand, some 2-arylbenzothiazole derivatives have been shown to possess potent inhibitory activity against human cancer cell lines[7] and some 2-aryl-1*H*-benzimidazoles have been reported to possess inotropic activity due at least in part to their Ca^{2+}-sensitizing effect.[8] Other 2-arylazoles containing two heteroatoms such as some 2-aryl-1*H*-imidazoles have been described as antagonists of the cannabinoid CB_1 receptor,[9] selective COX-2 inhibitors,[10] cytotoxic agents against a variety of cancer cell lines[11] or as neuropeptide Y5 antagonists.[12] Finally, several 2-arylbenzoxazoles have been shown to be heparanase inhibitors[13] and some 2-arylthiazoles have been reported to be hepatotoxic agents.[14]

The biological activities of these azoles have made them popular synthetic targets. Numerous synthetic methods, however, involve the construction of the azole ring by heteroannulation processes,[7b,8,12,14a,15–20] which frequently require the preparation of the starting materials by multi-step reaction sequences. Other useful methods for the synthesis of 2-arylazole derivatives are based on the construction of the heteroaryl–aryl bond at the 2-position of these heterocycles by Pd-catalyzed cross-coupling reactions between aryl halides or pseudohalides and 2-azolyl organometallics or between arylmetals and 2-haloazoles.[21–24] However, these procedures, in which the coupling partners are both activated, often involve several steps for preactivation of the coupling partners. Thus, this methodology is time-consuming and economically inefficient as it requires the installation and subsequent disposal of stoichiometric amounts of activating agents.

A very attractive, convenient and practical alternative to these synthetic approaches involves the intermolecular azolyl–aryl bond formation by transition metal-mediated C-2 arylation of azoles **1** with aryl halides or pseudohalides **2** in the presence of a suitable ligand and an inorganic base (Scheme 1).[25] This methodology, which addresses issues of synthetic efficiency and reaction processing, in the case of the regioselective Pd-catalyzed C-2 arylation reactions of 1-methyl-1*H*-imidazole[25a] and 1-aryl-1*H*-imidazoles[11] with aryl halides, also requires the use 2 equiv of CuI as additive.



(Y = CH, N; Z = NMe, NAr, NH, NAc, NMs, NBn, NSEM); (Y = N; Z = O); (Y = N; Z = S); (X = Br, I, OTf)

Scheme 1.

Keywords: Azoles; Direct arylation; Regioselectivity; Biologically active compounds; C–H bond activation.
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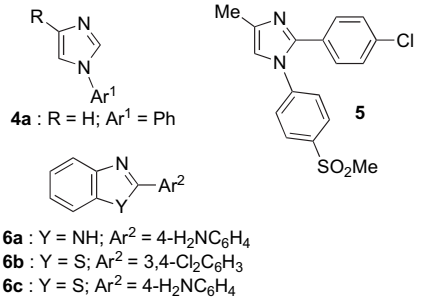
In the course of our studies into the synthesis and evaluation of the biological properties of vicinal diaryl substituted five-membered heterocycle derivatives[11,26] we recently developed a regioselective and efficient procedure to prepare 1,2-diaryl-1*H*-imidazoles through direct C-2 arylation of 1-aryl-1*H*-imidazoles with aryl halides in the presence of CuI and CsF and catalytic $Pd(OAc)_2$ in DMF at 140 °C under ligandless conditions.[11a] Next, we examined more deeply the reaction conditions under which to perform the direct C-2 arylation of 1-aryl-1*H*-imidazoles and other azoles and in a preliminary communication we reported that a variety of π-electron sufficient heteroarenes that included thiazole, oxazole, 1-aryl-1*H*-imidazoles, 1-methyl-1*H*-imidazole as well as free (NH)-imidazole, -benzimidazole and -indole can undergo effective and highly regioselective Pd- and Cu-mediated C-2 arylation with aryl iodides under base-free and ligandless conditions.[27] In this paper, we wish to disclose the full details and scope of this unprecedented and convenient methodology, which allows the use of substrates containing base-sensitive groups, such as the NH groups of imidazole, benzimidazole and indole, without their prior protection. Moreover, we describe the successful use of activated or unactivated aryl bromides in the synthesis of 2-aryl-1-phenyl-1*H*-imidazoles by one-pot domino HALEX[28] and Pd- and Cu-mediated arylation reactions of 1-phenyl-1*H*-imidazole (**4a**) under base-free and ligandless conditions. Finally, we report the applications of our novel protocol for the direct C-2 arylation of azoles to the preparation of the imidazole derivative **5**, which is a selective COX-2 inhibitor,[20d] 2-(4-aminophenyl)-1*H*-benzimidazole (**6a**), which is a key intermediate in the synthesis of a heparanase inhibitor[29] and some compounds with antimicrobial activities[30] and biologically active 2-arylbenzothiazoles **6b** and **6c**.



Compound **6b** is a potent topoisomerase II inhibitor[17b] and **6c** (CJM 126) is able to elicit biphasic growth inhibitory effects against a panel of estrogen receptor-positive and oestrogen receptor-negative human mammary cancer cell lines in vitro.[7c]

2. Results and discussion

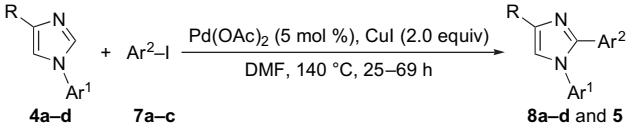
We initiated the study by examining the reaction of **4a** with 2 equiv of 4-iodoanisole (**7a**) in DMF at 140 °C in the presence of 5 mol % $Pd(OAc)_2$ and 2 equiv of CuI and found that after 26 h the reaction was complete and had cleanly and regioselectively furnished the required 2-aryl-1*H*-imidazole **8a** in 70% isolated yield (Table 1, entry 1). Interestingly, this yield was significantly higher than that we previously obtained in a similar reaction performed in the presence of 2 equiv of CsF.[11a] It is also worth mentioning that the crude reaction mixture did not contain the biaryl derivative derived from homocoupling of **7a** or the triaryl derivative that would have resulted from the C-2 and C-5 arylations of **4a**. In contrast, these byproducts contaminated the crude reaction mixture obtained from the Pd- and Cu-mediated reaction of **4a** with **7a**, which was performed in the presence of CsF.[11a]

Next, we examined the possible influence of some reaction parameters on the outcome of this C-2 arylation and found that when the amount of CuI was reduced from 2 equiv to 0.5 equiv the reaction time was much longer (126 h) and that compound **8a** was obtained in a lower yield (49%). Moreover, we observed that no reaction occurred using toluene, xylene, dioxane, diglyme or DMSO as solvent in place of DMF. In contrast, the use of a solvent such as DMF, DMA or DMPU possessing mildly basic characteristics proved to be necessary. However, DMF proved to be the solvent of choice.

The good result obtained in the preparation of **8a** from **4a** and **7a** using the experimental conditions reported in entry 1 of Table 1 prompted us to extend the procedure used in this entry to the synthesis of other 1,2-diaryl-1*H*-imidazoles. Entries 2–5 of Table 1 summarize the good results obtained in the regioselective preparation of compounds **8b–d** and **5** using these experimental conditions.

We also investigated the use of aryl bromides **9** in the Pd- and Cu-mediated C-2 arylation of **4a** under base-free and

Table 1. Pd- and Cu-mediated C-2 arylation of 1-aryl-1*H*-imidazoles **4** with aryl iodides **7**



Entry	Reagents					Reaction time[a] (h)	Product	Isolated yield[b] (%)
	4	R	Ar^1	**7**	Ar^2		**8** or **5**	
1	**4a**	H	Ph	**7a**	4-$MeOC_6H_4$	26	**8a**	70 (62)
2	**4a**	H	Ph	**7b**	Ph	69	**8b**	76 (55)
3	**4b**	H	4-$MeOC_6H_4$	**7a**	4-$MeOC_6H_4$	48	**8c**	66 (38)
4	**4c**	H	4-$MeSO_2C_6H_4$	**7a**	4-$MeOC_6H_4$	25	**8d**	84 (67)
5	**4d**[c]	Me	4-$MeSO_2C_6H_4$	**7c**	4-ClC_6H_4	48	**5**	78 (62)

[a] The reactions were complete after the reaction times indicated.
[b] The values in parenthesis are referred to the isolated yields obtained in the corresponding reactions performed in the presence of 2 equiv of CsF (Ref. 11a).
[c] This compound was not regioisomerically pure. It was contaminated by ca. 20% of 5-methyl-1-[(4-methylsulfonyl)phenyl]-1*H*-imidazole (**4e**).

ligandless conditions, but, in a test involving the reaction of **4a** with 2 equiv of bromobenzene (**9a**) in DMF at 140 °C, 1,2-diphenyl-1*H*-imidazole (**8b**) was obtained in only 41% GLC yield after 161 h (Table 2, entry 1). A similar modest GLC yield was obtained when the reaction between **4a** and 4-bromobenzotrifluoride (**9b**) was carried out using analogous experimental conditions (Table 2, entry 2).

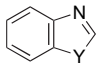
Nevertheless, we found that the results of the reaction of **4a** with **9a** could be improved by addition of 4 equiv of NaI to the reagents. In fact, compound **8b** was so obtained in 47% isolated yield after 165 h at 140 °C (Table 2, entry 3). A further improvement of the yield of **8b** was obtained using KI in place of NaI. In fact, under these conditions **8b** was obtained in 57% yield (Table 2, entry 4). Interestingly, these experimental conditions allowed us to prepare **8e** in 72% yield from **4a** and the activated aryl bromide **9b** (Table 2, entry 5), but they proved to be unsuitable for the C-2 arylation of **4a** with the deactivated aryl bromide **9c** (Table 2, entry 6). It should also be noted that, despite their very long reaction times and the unexpected presence in the final reaction mixtures of significant amounts of aryl iodides **7** corresponding to the aryl bromides used as reagents, the reactions, which provided compounds **8b** and **8e** were not complete.

Iodides **7** most likely derived from an HALEX reaction between NaI or KI and aryl bromides **9** and compounds **8b** and **8e** were likely formed, at least in part, by C-2 arylation reactions involving iodides **7**. On the other hand, the result that the arylation reactions were not complete could be explained taking into account that the presence of a large molar excess of iodide anions reduces the electrophilicity of the arylpalladium halide species[31] undergoing transmetallation with the 1-phenyl-1*H*-imidazol-2-ylcopper species, which presumably are intermediates of the catalytic cycle of these arylations.

Next, the protocol developed for the Pd- and Cu-mediated synthesis of compounds **8** from 1-aryl-1*H*-imidazoles **4** and aryl iodides **7** was investigated for the regioselective C-2 arylation of several other π-electron sufficient heteroarenes that included 1-methyl-1*H*-imidazole (**10a**), 1-benzyl-1*H*-imidazole (**10b**), free (NH)-imidazole (**10c**), 5-phenyl-1*H*-imidazole (**10d**), thiazole (**10e**), oxazole (**10f**), benzothiazole (**11a**) and free (NH)-benzimidazole (**11b**).

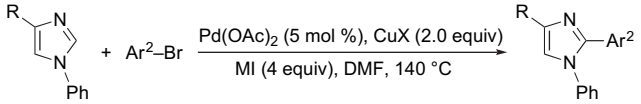
Tables 3 and 4 summarize the results obtained in the highly regioselective Pd- and Cu-mediated C-2 arylation reactions of these heterocycles with unactivated, activated and deactivated aryl iodides **7** under base-free and ligandless conditions. Notably, the reactions occurred in high yields and were very clean. In fact, the crude reaction mixtures obtained from azoles **10** and iodides **7** contained no regioisomers of the required 2-arylheteroarenes **12**[32] and, in the case of free (NH)-imidazole (**10c**) and -benzimidazole (**11b**) were also free of *N*-aryl derivatives.

10a : Y = NMe; R = H
10b : Y = NBn; R = H
10c : Y = NH; R = H
10d : Y = NH; R = Ph
10e : Y = S; R = H
10f : Y = O; R = H



11a : Y = S
11b : Y = NH

Table 2. C-2 arylation of 1-phenyl-1*H*-imidazole (**4a**) with aryl bromides **9**

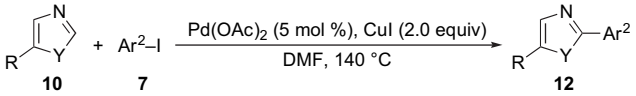


4a : R = H **9** **8** : R = H

Entry[a]	Aryl bromide		MI	Reaction time[a] (h)	Product	Isolated yield[b] (%)
	9	Ar^2			**8**	
1	**9a**	Ph	—	161	**8b**	(41)
2	**9b**	4-$CF_3C_6H_4$	—	115	**8e**	(35)
3	**9a**	Ph	NaI	165	**8b**	47
4	**9a**	Ph	KI	164	**8b**	57
5	**9b**	4-$CF_3C_6H_4$	KI	166	**8e**	72
6	**9c**	4-$MeOC_6H_4$	KI	166	—	—

[a] The reactions were run using 1 mmol of **4a** and 2 mmol of aryl bromides **9**.
[b] The values in parenthesis are referred to GLC yield (naphthalene was used as internal standard).

Table 3. Synthesis of 2-arylazoles **12** by C-2 arylation of azoles **10**

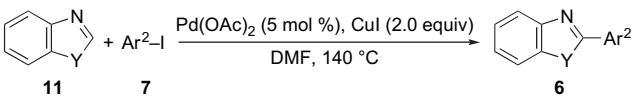


10 **7** **12**

Entry[a,b]	Reagents					Reaction time[a] (h)	Product	Isolated yield[b] (%)
	10	R	Y	**7**	Ar^2		**12**	
1	**10a**	H	NMe	**7a**	4-$MeOC_6H_4$	48	**12a**	99
2	**10b**	H	NBn	**7a**	4-$MeOC_6H_4$	48	**12b**	87
3	**10c**	H	NH	**7a**	4-$MeOC_6H_4$	48	**12c**	53
4[c]	**10c**	H	NH	**7a**	4-$MeOC_6H_4$	52	**12c**	84
5	**10c**	H	NH	**7b**	Ph	48	**12d**	89
6	**10c**	H	NH	**7d**	4-$CF_3C_6H_4$	48	**12e**	84
7	**10c**	H	NH	**7e**	2-MeC_6H_4	48	**12f**	47
8	**10d**	Ph	NH	**7a**	4-$MeOC_6H_4$	72	**12g**	47
9	**10e**	H	S	**7a**	4-$MeOC_6H_4$	48	**12h**	84
10	**10f**	H	O	**7a**	4-$MeOC_6H_4$	48	**12i**	23
11[d]	**10f**	H	O	**7a**	4-$MeOC_6H_4$	74	**12i**	74

[a] Unless otherwise reported the reactions were run using 1 mmol of **10** and 2 mmol of iodides **7** in 5 mL of DMF at 140 °C.
[b] The conversion of all reactions reported was quantitative.
[c] This reaction was run using 2 mmol of **10c** and 1 mmol of **7a**.
[d] This reaction was run using 3 mmol of **10f** and 1 mmol of **7a**.

Table 4. Synthesis of 2-arylbenzoazoles **6** by C-2 arylation of compounds **11**



11 **7** **6**

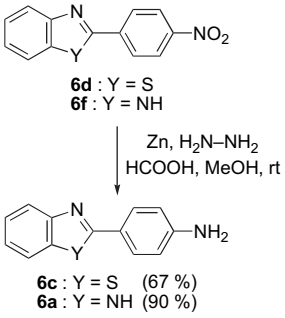
Entry[a]	Reagents				Reaction time (h)	Product	Isolated yield (%)
	11	Y	**7**	Ar^2		**6**	
1	**11a**	S	**7f**	4-$NO_2C_6H_4$	115	**6d**	85
2	**11a**	S	**7g**	3,4-$Cl_2C_6H_3$	48	**6b**	87
3	**11b**	NH	**7a**	4-$MeOC_6H_4$	48	**6e**	81
4	**11b**	NH	**7f**	4-$NO_2C_6H_4$	96	**6f**	89

[a] The reactions were run using 1 mmol of **11** and 2 mmol of iodides **7** in 5 mL of DMF. After the period of time reported here the conversion of the reactions was quantitative.

On the other hand, the use of ligandless conditions prevented the formation of byproducts that might derive from scrambling of the aryl moieties of iodides **7** with the organic group of the ligands, which had been found in the crude reaction mixtures obtained from the Pd-catalyzed arylation of 1-aryl-1*H*-imidazoles **4** in the presence of triarylphosphines.[26c]

It should also be noted that in entries 4 and 11 of Table 3, where a molar excess of imidazole (**10c**) and oxazole (**11**), respectively, was reacted with aryl iodide **7a**, the required 2-arylazoles were obtained in yields significantly higher than those of the same reactions performed using a molar excess of **7a** (Table 3, entries 3 and 10, respectively). However, despite these good results, we preferred to perform the other arylation reactions reported in Tables 3 and 4 using a molar excess of aryl iodides **7** since the purification of the reaction mixtures and isolation of the required chemically pure 2-arylazoles proved to be easier by using these experimental conditions.

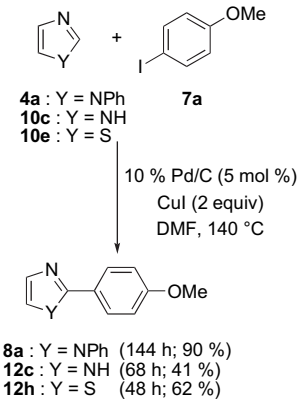
It is also worth noting that compound **6b**, which was obtained in 87% yield by arylation of **11a** with **7g** (Table 4, entry 2), is a topoisomerase II inhibitor.[17b] On the other hand, compounds **6d** and **6f**, which were prepared in 85 and 89% yield, respectively, by arylation of **11a** and **11b** with **7f** (Table 4, entries 1 and 4, respectively), could be selectively reduced by using zinc dust and hydrazinium monoformate[33] to give the biologically active derivatives **6c**[7c] and **6a**[29,30] in 67 and 90% yield, respectively (Scheme 2). Recently, compound **6c** has been used to prepare a rhenium complex that enters MCF-7 breast cancer cell lines and the analogous radioactive ^{99m}Tc complex that produces fast blood and soft tissue clearance when administered to healthy mice.[34] Compounds **6a** and **6c** were so prepared since they could not be synthesized by Pd- and Cu-mediated direct arylation of benzimidazole (**11b**) and benzothiazole (**11a**), respectively, with 4-iodoaniline. In fact, these reactions, which provided black reaction mixtures, did not produce significant amounts of the required 2-(4-aminophenyl)benzoazoles.



Scheme 2.

We also performed a preliminary study aimed at evaluating the possibility of using Pd/C in place of $Pd(OAc)_2$ in the regioselective Pd- and Cu-mediated C-2-arylation of azoles **4a**, **10c** and **10e**. In fact, Pd/C is an inexpensive heterogeneous catalyst, which can be removed by filtration at the end of the reaction and, thus, does not contaminate the reaction product. Moreover, it can be recycled for another reaction.[35]

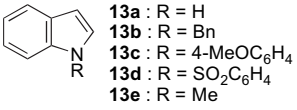
Scheme 3 summarizes the results obtained in this preliminary investigation.



Scheme 3.

Thus, the reaction of **4a** with 2 equiv of **7a** in DMF at 140 °C for 144 h in the presence of 10% Pd/C (5 mol %) and CuI (2 equiv) gave **8a** in a yield (90%) higher than that obtained using $Pd(OAc)_2$ in place of Pd/C (Table 1, entry 1). However, the yields of compounds **12c** and **12h** (41 and 62%, respectively), which were prepared using Pd/C as the catalyst proved to be lower than those obtained in the analogous reactions performed under homogeneous conditions (Table 3, entries 4 and 9, respectively).

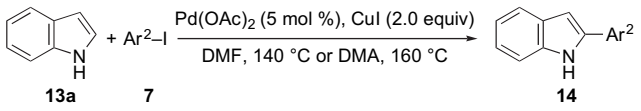
Finally, it appeared to be of interest to investigate the possibility of using our novel protocol for the Pd- and Cu-mediated C-2 arylation of azoles with aryl iodides under base-free and ligandless conditions also for the selective C-2 arylation of free (NH)-indole (**13a**). In fact, even though all results that we had obtained for the arylation reactions of 1,3-azoles using this protocol might indicate that the presence and participation of a basic pyridine-like nitrogen atom was required in the heteroarenes, which were used as substrates for the arylation reaction, we speculated that the presence of a pyridine-like nitrogen atom might be unnecessary provided that the arylation reaction was performed in a solvent such as DMF or DMA with mildly basic characteristics.[36]



As we had hoped for, we found that **13a** is able to react with iodide **7a** in DMF at 140 °C in the presence of 5 mol % $Pd(OAc)_2$ and 2 equiv of CuI to give 2-aryl-1*H*-indole **14a** in 35% isolated yield (Table 5, entry 1). Interestingly, when the reaction between 2 equiv of **7a** and **13a** was performed in DMA at 160 °C, instead of in DMA at 140 °C, compound **14a** was obtained in 54% isolated yield (Table 5, entry 2).

However, this compound was isolated in only 10% yield from the Pd- and Cu-mediated reaction of 2 equiv of **13a** with **7a** (Table 5, entry 3). On the other hand, the Pd- and

Table 5. Pd- and Cu-mediated C-2 arylation of free (NH)-indole (**13a**)



13a **7** **14**

Entry[a]	Reagents		Solvent	Reaction temperature (°C)	Product	Isolated yield (%)
	7	Ar^2			**14**	
1	**7a**	4-$MeOC_6H_4$	DMF	140	**14a**	35
2	**7a**	4-$MeOC_6H_4$	DMA	160	**14a**	53
3[b]	**7a**	4-$MeOC_6H_4$	DMA	160	**14a**	10
4	**7b**	Ph	DMA	160	**14b**	29
5	**7d**	4-$CF_3C_6H_4$	DMA	160	**14c**	33

[a] Unless otherwise reported the reactions were run using 1 mmol of **13a** and 2 mmol of iodides **7** in 5 mL of DMF or DMA for 48 h.
[b] The reaction was run using a 2/1 molar ratio between **13a** and **7a**.

Cu-mediated reaction of **13a** with 2 equiv of iodides **7b** and **7d** in DMA at 160 °C gave compounds **14b** and **14c** in 29 and 33% yield, respectively (Table 5, entries 4 and 5, respectively). Unfortunately, the protocol used to prepare 2-aryl-1*H*-indoles **14a–d** proved to be unsuitable for the arylation of 1-benzyl-1*H*-indole (**13b**), 1-(4-methoxyphenyl)-1*H*-indole (**13c**), 1-(benzensulfonyl)-1*H*-indole (**13d**) and 1-methyl-1*H*-indole (**13e**). In fact, the required 2-aryl-1-substituted-1*H*-indoles were obtained in very low yields.

3. Conclusions

We have disclosed an efficient and reliable general method for the direct and highly regioselective C-2 arylation of azoles with aryl iodides, which does not produce byproducts and thus allow to obtain the required 2-arylazoles in high purity. The unprecedented reaction conditions of this new procedure, which do not involve the use of a base, can also be employed for the arylation of substrates containing base-sensitive groups such as the NH groups in imidazole, benzimidazole and indole, without their prior protection. This new arylation protocol, which is suitable for medicinal chemistry where a wide diversity of products is desired, has been applied for the preparation of a large variety of 2-arylazoles that include three biologically active compounds and a key intermediate of a heparanase inhibitor and some antimicrobial products. Moreover, we have developed a one-pot domino procedure for the synthesis of 2-aryl-1-phenyl-1*H*-imidazoles from 1-phenyl-1*H*-imidazole and activated or unactivated aryl bromides.

The results presented in this paper also indicate that the Pd- and Cu-mediated arylation, under base-free and ligandless conditions, may involve also heterocycles that do not contain a basic pyridine-like nitrogen atom, provided that this reaction is performed in a solvent with mildly basic characteristics. Nevertheless, the Pd- and Cu-mediated C-2 arylation of free (NH)-indole with aryl iodides under base-free and ligandless conditions provides 2-aryl-1*H*-indoles in modest yields. In our opinion, this result can be rationalized taking into account that a significant lowering of the pH of the reaction mixture, due to the development of iodidric acid, is produced in the Pd- and Cu-mediated C-2 arylation of free (NH)-indole and its 1-substituted derivatives under these experimental conditions and that acidic conditions promote the oligomerization of indole.[37]

Finally, regarding the mechanism of the arylation reactions of the azoles used in this paper as substrates, we propose that it involves, as we recently reported,[11a] the formation of an organocopper(I) derivative followed by a transmetallation reaction with an arylpalladium(II) halide species and a reductive elimination. On the other hand, coordination of heterocycles **4**, **10** and **11** to CuI to form π-complexes might significantly lower the pK_a of their C–H bonds at position 2 and facilitate their conversion into C–Cu bonds.[38] However, at present, a reaction mechanism involving the presence of organopalladium(II) and organopalladium(IV) species and organocopper(I) derivatives cannot be excluded.[39]

Studies on further applications of our direct arylation protocol for the synthesis of compounds of interest in medicinal chemistry are in progress.

4. Experimental

4.1. General

Melting points are uncorrected. Merck precoated 60 F_{254} aluminium silica gel sheets were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani DDS 1000 data station. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column (30 m× 0.25 mm i.d.) and an Alltech AT-35 bonded FSOT column (30 m×0.25 mm i.d.). Purifications by MPLC on silica gel (Merck silica gel 60, particle size 0.015–0.040 mm) were performed on a Büchi B-680 system using a Knauer K-2400 differential refractometer as detector. Electron impact mass spectra were measured at 70 eV by GLC/MS. GLC/MS analyses were performed using an Agilent 6890 Network GC system interfaced with an Agilent 5973 Network mass selective detector. NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer and a Varian Gemini 300 MHz spectrometer with TMS as the internal reference. All reactions were performed in flame dried glassware under a positive atmosphere of argon by standard syringe, cannula and septa techniques. 1-Phenyl-1*H*-imidazole (**4a**), 4-iodoanisole (**7a**), iodobenzene (**7b**), 1-chloro-4-iodobenzene (**7c**), 4-iodobenzotrifluoride (**7d**), 2-iodotoluene (**7e**), 1-iodo-4-nitrobenzene (**7f**), 1,2-dichloro-4-iodobenzene (**7g**), bromobenzene (**9a**), 4-bromobenzotrifluoride (**9b**), 4-bromoanisole (**9c**), 1-methyl-1*H*-imidazole (**10a**), 1-benzyl-1*H*-imidazole (**10b**), imidazole (**10c**), 4(5)-phenyl-1*H*-imidazole (**10d**), thiazole (**10e**), oxazole (**10f**), benzothiazole (**11a**), benzimidazole (**11b**) and indole (**13a**) were commercially available. The following compounds were prepared according to the literature: 1-(4-methoxyphenyl)-1*H*-imidazole (**4b**),[11a] 1-[(4-methylsulfonyl)phenyl]-1*H*-imidazole (**4c**),[11a] 4-methyl-1-[(4-methylsulfonyl)phenyl]-1*H*-imidazole (**4d**),[11a] 1-benzyl-1*H*-indole (**13b**),[40] 1-(4-methoxyphenyl)-1*H*-indole (**13c**)[41] and 1-phenylsulfonyl-1*H*-indole (**13d**).[42] Compound **4d**, which was contaminated by ca. 20% of 5-methyl-1-[(4-methylsulfonyl)phenyl]-1*H*-imidazole (**4e**),

was used without any further purification in a subsequent Pd- and Cu-mediated arylation reaction with iodide **7c**.

4.2. General procedure for the Pd- and Cu-mediated C-2 arylation of 1-aryl-1*H*-imidazoles 4a–d, azoles 10a–f and benzoazoles 11a,b with aryl iodides 7

Compound **4**, **10** or **11** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), CuI (0.38 g, 2.0 mmol) and (if a solid) aryl iodide **7** (2.0 mmol) were placed in the reaction vessel under a stream of argon. The reaction vessel equipped with a silicon septum, a reflux condenser and a magnetic stirrer was evacuated and back-filled with argon, and this sequence was repeated twice. Deaerated DMF (5 mL) and (if a liquid) the aryl iodide **7** (2.0 mmol) were then added successively by syringe under a stream of argon. The resulting mixture was stirred at 140 °C under argon for the period of time reported in Tables 1, 3 and 4. The degree of completion of the reaction was evaluated by GLC and GLC/MS analyses of a sample of the crude reaction mixture. After being cooled to room temperature the reaction mixture was diluted with AcOEt and poured into a saturated aqueous NH_4Cl solution and the resulting mixture was stirred in the open air for 0.5 h and then extracted with AcOEt. The organic extract was washed with water, dried, filtered trough Celite and the filtrate was concentrated under reduced pressure. The residue was purified by MPLC on silica gel and the chromatographic fraction containing the required compound were collected and concentrated under reduced pressure. This procedure was employed to prepare compounds **8a–d** and **5** (Table 1, entries 1–5), 2-arylazoles **12a–i** (Table 2, entries 1–11) and 2-arylbenzoazoles **6d**, **6b** and **6e** (Table 4, entries 1–3). GLC analysis showed that all these compounds had chemical purity higher than 98%. However, the crude reaction product obtained in entry 4 of Table 4 was purified by recrystallization. Compound **6f**, which was so obtained had 92% chemical purity.

4.2.1. 2-(4-Methoxyphenyl)-1-phenyl-1*H*-imidazole (8a). The crude reaction product obtained in entry 1 of Table 1 by Pd- and Cu-mediated reaction of **4a** with **7a** was purified by MPLC on silica gel with a mixture of AcOEt and toluene (50:50+0.1% Et_3N) as eluent and subsequent treatment with 3-(mercaptopropyl)-functionalized silica gel to give **8a** (0.17 g, 70%) as a pale yellow solid. Mp 125–127 °C (lit.[11a] mp 125–127 °C). EIMS, *m/z* 251 (17), 250 (100), 249 (70), 235 (13), 206 (26). ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 3H), 7.37 (m, 2H), 7.30 (br s, 1H), 7.24 (m, 2H), 7.14 (br s, 1H), 6.80 (m, 2H), 3.78 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.3, 146.1, 138.1, 130.2 (2C), 129.7 (2C), 128.6, 127.0, 125.8 (2C), 122.5, 121.3, 113.6 (2C), 55.2. The physical and spectral properties of this compound were in good agreement with those reported for **8a** prepared by Pd- and Cu-mediated reaction of **4a** with **7a** in DMF at 140 °C in the presence of CsF under ligandless conditions.[11a]

4.2.2. 1,2-Diphenyl-1*H*-imidazole (8b). The crude reaction product obtained in entry 2 of Table 1 by Pd- and Cu-mediated reaction of **4a** with **7b** was purified by MPLC on silica gel with a mixture of AcOEt and toluene (50:50+0.1% Et_3N) as eluent and subsequent treatment with 3-(mercaptopropyl)-functionalized silica gel to give **8b** (0.17 g, 76%) as a colourless solid. Mp 78–79 °C (lit.[11a] mp 77–79 °C). EIMS, *m/z* 221 (14), 220 (90), 219 (100), 193 (12), 90 (11). ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 5H), 7.33 (d, J=1.3 Hz, 1H), 7.27 (m, 5H), 7.19 (d, J=1.3 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 146.2, 138.0, 129.7 (2C), 129.5, 129.1, 128.8 (2C), 128.6, 128.4 (2C), 127.5, 125.9 (2C), 122.9. The physical and spectral properties of this compound were in good agreement with those reported for **8b** prepared by Pd- and Cu-mediated reaction of **4a** with **7b** in DMF at 140 °C in the presence of CsF under ligandless conditions.[11a]

4.2.3. 1,2-Bis(4-methoxyphenyl)-1*H*-imidazole (8c). The crude reaction product obtained in entry 3 of Table 1 by Pd- and Cu-mediated reaction of **4b** with **7a** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (98:2) as eluent and subsequent treatment with 3-(mercaptopropyl)-functionalized silica gel to give **8c** (0.19 g, 66%) as a colourless solid. Mp 107–109 °C (lit.[11a] mp 107–109 °C). EIMS, *m/z* 281 (18), 280 (100), 279 (33), 265 (20), 147 (17). ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J=8.3 Hz, 2H), 7.28 (br s, 1H), 7.16 (m, 2H), 7.09 (br s, 1H), 6.92 (m, 2H), 6.81 (d, J=8.3 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.4, 159.7, 146.3, 131.0, 130.1 (2C), 127.2 (2C), 126.0, 122.8, 121.0, 114.7 (2C), 113.9 (2C), 55.6, 55.3. The physical and spectral properties of this compound were in good agreement with those reported for **8c** prepared by Pd- and Cu-mediated reaction of **4b** with **7a** in DMF at 140 °C in the presence of CsF under ligandless conditions.[11a]

4.2.4. 2-(4-Methoxyphenyl)-1-[(4-methylsulfonyl)-phenyl]-1*H*-imidazole (8d). The crude reaction product obtained in entry 4 of Table 1 by Pd- and Cu-mediated reaction of **4c** with **7a** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (98:2) as eluent and subsequent treatment with 3-(mercaptopropyl)-functionalized silica gel to give **8d** (0.28 g, 84%) as a colourless solid. Mp 154–156 °C (lit.[11a] mp 154–155 °C). EIMS, *m/z* 329 (22), 328 (100), 327 (57), 248 (28), 148 (86). ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.42 (m, 2H), 7.29 (m, 3H), 7.18 (s, 1H), 6.82 (m, 2H), 3.80 (s, 3H), 3.09 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.4, 146.8, 142.8, 140.0, 130.4 (2C), 129.0 (3C), 126.4 (2C), 121.9, 121.4, 114.1 (2C), 55.3, 44.4. The physical and spectral properties of this compound were in good agreement with those reported for **8d** prepared by Pd- and Cu-mediated reaction of **4c** with **7a** in DMF at 140 °C in the presence of CsF under ligandless conditions.[11a]

4.2.5. 4-Methyl-2-(4-chlorophenyl)-1-[(4-methylsulfonyl)phenyl]-1*H*-imidazole (5). The crude reaction product obtained in entry 4 of Table 1 by Pd- and Cu-mediated reaction of **4d** with **7c** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (98:2) as eluent and subsequent treatment with 3-(mercaptopropyl)-functionalized silica gel to give **8d** (0.27 g, 78%) as a colourless solid. Mp 60–61 °C (lit.[11a] mp 60 °C). EIMS, *m/z* 348 (38), 347 (33), 346 (100), 345 (38), 226 (21). ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.38 (m, 2H), 7.31 (m, 2H), 7.27 (m, 2H), 6.94 (s, 1H), 3.09 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.9, 142.4, 140.1, 138.9, 135.4,

130.1 (2C), 129.1 (2C), 128.9 (2C), 127.6, 126.1 (2C), 119.1, 44.4, 13.4. The physical and spectral properties of this compound were in good agreement with those reported for **5** prepared by Pd- and Cu-mediated reaction of **4d** with **7a** in DMF at 140 °C in the presence of CsF under ligandless conditions.[11a]

4.2.6. 2-(4-Methoxyphenyl)-1-methyl-1*H*-imidazole (12a). The crude reaction product obtained in entry 1 of Table 3 by Pd- and Cu-mediated reaction of **10a** with **7a** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (96:4) as eluent and subsequent treatment with 3-(mercaptopropyl)-functionalized silica gel to give **12a** (0.19 g, 99%) as a yellow oil. EIMS, *m*/*z* 188 (100), 187 (93), 173 (16), 172 (22), 145 (17). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.08 (d, J=1.0 Hz, 1H), 6.97 (m, 2H), 6.92 (d, J=1.0 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.9, 147.8, 130.0 (2C), 128.1, 123.2, 122.0, 113.9 (2C), 55.3, 34.4. The spectroscopic data of this compound were in agreement with those previously reported.[43]

4.2.7. 1-Benzyl-2-(4-methoxyphenyl)-1*H*-imidazole (12b). The crude reaction product obtained in entry 2 of Table 3 by Pd- and Cu-mediated reaction of **10b** with **7a** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (97:3) as eluent and subsequent treatment with 3-(mercaptopropyl)-functionalized silica gel to give **12b** (0.23 g, 87%) as a pale orange oil. EIMS, *m*/*z* 265 (19), 264 (98), 174 (12), 173 (100), 91 (34). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.30 (m, 3H), 7.14 (d, J=1.2 Hz, 1H), 7.06 (m, 2H), 6.90 (m, 3H), 5.16 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.0, 148.1, 137.1, 130.1 (2C), 128.9 (2C), 128.7 (2C), 127.8, 126.5 (2C), 114.0 (2C), 55.2, 50.3. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10. Found: C, 77.31; H, 6.03.

4.2.8. 2-(4-Methoxyphenyl)-1*H*-imidazole (12c). The crude reaction product obtained in entry 4 of Table 3 by Pd- and Cu-mediated reaction of **10c** with **7a** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (95:5) as eluent to give **12c** (0.15 g, 84%) as a colourless solid. Mp 152–153 °C (lit.[43] mp 160–161 °C). EIMS, *m*/*z* 175 (11), 174 (100), 159 (46), 147 (7), 131 (29). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.04 (br s, 1H), 7.92 (m, 2H), 7.10 (s, 2H), 6.97 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 160.8, 147.3, 127.5 (2C), 124.9, 123.6, 115.0, 55.7. Anal. Calcd for $C_{10}H_{10}N_2$: C, 68.95; H, 5.79. Found: C, 68.87; H, 5.64. The spectral data of this compound were in agreement with those previously reported.[43]

4.2.9. 2-Phenyl-1*H*-imidazole (12d). The crude reaction product obtained in entry 5 of Table 3 by Pd- and Cu-mediated reaction of **10c** with **7b** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (95:5) as eluent to give **12d** (0.13 g, 89%) as a pale yellow solid. Mp 141–143 °C (lit.[44] mp 140–142 °C). EIMS, *m*/*z* 145 (10), 144 (100), 117 (41), 90 (17), 77 (8). ^{1}H NMR (300 MHz, CD_3OD) δ 7.86 (m, 2H), 7.41 (m, 3H), 7.13 (m, 2H). ^{13}C NMR (75.5 MHz, CD_3OD) δ 148.1, 131.5, 129.9 (2C), 129.7 (2C), 126.4 (2C), 123.8. The spectral properties of this compound were in agreement with those of commercially available **12d**.

4.2.10. 2-[(4-Trifluoromethyl)phenyl]-1*H*-imidazole (12e). The crude reaction product obtained in entry 6 of Table 3 by Pd- and Cu-mediated reaction of **10c** with **7d** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (95:5) as eluent to give **12e** (0.18 g, 84%) as a colourless solid. Mp 219–221 °C (lit.[40] mp 248 °C). EIMS, *m*/*z* 213 (11), 212 (100), 193 (9), 185 (33), 158 (13). ^{1}H NMR (300 MHz, CD_3OD) δ 8.03 (m, 2H), 7.74 (m, 2H), 7.20 (s, 2H). ^{13}C NMR (75.5 MHz, CD_3OD) δ 146.5, 135.0, 131.3 (d, J_{C-F}=32 Hz), 126.9, (q, J_{C-F}= 3.6 Hz, 2C), 126.8 (2C), 124.8. Anal. Calcd for $C_{10}F_3H_6N_2$: C, 56.88; H, 2.86. Found: C, 56.69; H, 3.10.

4.2.11. 2-(2-Methylphenyl)-1*H*-imidazole (12f). The crude reaction product obtained in entry 7 of Table 3 by Pd- and Cu-mediated reaction of **10c** with **7e** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (96:4) as eluent to give **12f** (75 mg, 47%) as a colourless solid. Mp 138–139 °C (lit.[45] mp 136 °C). EIMS, *m*/*z* 159 (11), 158 (96), 157 (100), 130 (17), 103 (7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J=7.5 Hz, 1H), 7.21 (m, 2H), 7.10 (t, J=7.5 Hz, 1H), 6.91 (m, 2H), 2.36 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.0, 136.5, 130.9, 130.5, 129.2, 128.6 (2C), 125.7, 122.3, 20.6. Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37: Found: C, 75.86; H, 6.23.

4.2.12. 2-(4-Methoxyphenyl)-5-phenyl-1*H*-imidazole (12g). The crude reaction product obtained in entry 8 of Table 3 by Pd- and Cu-mediated reaction of **10d** with **7a** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (99:1) as eluent to give **12g** (0.12 g, 47%) as a yellow solid. Mp 160–162 °C. EIMS, *m*/*z* 251 (19), 250 (100), 235 (41), 207 (13), 89 (8). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.71 (d, J=6.9 Hz, 2H), 7.37–7.20 (m, 4H), 6.85 (m, 2H), 3.78 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.1, 147.4, 138.8, 132.7, 128.7 (2C), 126.9 (3C), 124.9 (2C), 123.0, 116.9, 114.2 (2C), 55.3. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64. Found: C, 76.69; H, 5.60.

4.2.13. 2-(4-Methoxyphenyl)thiazole (12h). The crude reaction product obtained in entry 9 of Table 3 by Pd- and Cu-mediated reaction of **10e** with **7a** was purified by MPLC on silica gel with a mixture of hexane and AcOEt (80:20) as eluent to give **12h** (0.16 g, 84%) as a pale yellow oil. EIMS, *m*/*z* 192 (12), 191 (100), 176 (43), 148 (15), 58 (21). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.79 (d, J=3.2 Hz, 1H), 7.23 (d, J=3.2 Hz, 1H), 6.93 (m, 2H), 3.82 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.4, 161.2, 143.5, 128.2 (2C), 126.7, 118.0, 114.4 (2C), 55.5. The spectral data of this compound were in agreement with those previously reported.[43]

4.2.14. 2-(4-Methoxyphenyl)oxazole (12i). The crude reaction product obtained in entry 11 of Table 3 by Pd- and Cu-mediated reaction of **10f** with **7a** was purified by MPLC on silica gel with a mixture of hexane and AcOEt (80:20) as eluent to give **12i** (0.13 g, 74%) as a pale yellow oil. EIMS, *m*/*z* 176 (11), 175 (100), 132 (25), 120 (21), 91 (16). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.65 (d, J=0.7 Hz, 1H), 7.19 (d, J=0.7 Hz, 1H), 6.97 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.1, 161.4, 138.0, 128.1, 128.0 (2C), 120.3, 114.2 (2C), 55.4. The spectral data of this compound were in agreement with those previously reported.[42]

4.2.15. 2-(4-Nitrophenyl)benzothiazole (6d). The crude reaction product obtained in entry 1 of Table 4 by Pd- and Cu-mediated reaction of **11a** with **7f** was purified by MPLC on silica gel with a mixture of toluene and petroleum ether (70:30+0.1% Et_3N) as eluent and subsequent treatment with 3-(mercaptopropyl)-functionalized silica gel to give **6d** (0.22 g, 85%) as a pale yellow solid. Mp 226–228 °C (lit.[46] mp 228–230 °C). EIMS, *m/z* 257 (16), 256 (100), 226 (12), 210 (37), 209 (37). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (m, 2H), 8.26 (m, 2H), 8.13 (d, J=7.8 Hz, 1H), 7.96 (m, 1H), 7.54 (m, 1H), 7.48 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.1, 149.0, 139.2, 135.5, 128.3 (2C), 126.9, 126.2, 124.3 (2C), 123.9, 121.8 (2C). Anal. Calcd for $C_{13}H_8N_2O_2S$: C, 60.93; H, 3.14. Found: C, 60.83; H, 3.07.

4.2.16. 2-(3,4-Dichlorophenyl)benzothiazole (6b). The crude reaction product obtained in entry 2 of Table 4 by Pd- and Cu-mediated reaction of **11a** with **7g** was purified by MPLC on silica gel with a mixture of toluene and petroleum ether (20:80) as eluent and subsequent treatment with 3-(mercaptopropyl)-functionalized silica gel to give **6b** (0.24 g, 87%) as a colourless solid. Mp 115–116 °C (lit.[46] mp 117–118 °C). EIMS, *m/z* 283 (14), 282 (11), 281 (67), 280 (20), 279 (100). ^{1}H NMR (200 MHz, acetone-d_6) δ 8.27 (d, J=1.8 Hz, 1H), 8.12 (m, 1H), 8.05 (m, 2H), 7.74 (d, J=8.4 Hz, 1H), 7.53 (m, 2H). ^{13}C NMR (50.3 MHz, C_6D_6) δ 164.9, 154.6, 135.6, 135.0, 133.9, 133.7, 131.0, 129.3, 126.8, 126.6, 125.8, 124.0, 121.8. The ^{1}H NMR data of this compound were in agreement with those previously reported.[17b]

4.2.17. 2-(4-Methoxyphenyl)-1*H*-benzimidazole (6e). The crude reaction product obtained in entry 3 of Table 4 by Pd- and Cu-mediated reaction of **11b** with **7a** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (96:4) as eluent to give **6e** (0.18 g, 81%) as a pale yellow solid. Mp 215–217 °C (lit.[47] mp 224–229 °C). EIMS, *m/z* 225 (16), 224 (100), 209 (37), 181 (28), 90 (4). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (m, 2H), 7.57 (m, 2H), 7.19 (m, 2H), 7.12 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.5, 151.3, 127.9 (4C), 122.7, 121.7 (2C), 114.3 (4C), 55.2. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 77.98; H, 5.39. Found: C, 77.85; H, 5.24.

4.2.18. 2-(4-Nitrophenyl)-1*H*-benzimidazole (6f). The crude reaction product obtained in entry 4 of Table 4 by Pd- and Cu-mediated reaction of **11b** with **7f** was purified by recrystallization from Et_2O and EtOH to give **6f** (0.21 g, 89%) as a pale yellow solid. Mp 306–308 °C (lit.[48] mp 297–299). EIMS, *m/z* 240 (15), 239 (100), 209 (11), 193 (50), 192 (26). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (m, 4H), 7.67 (m, 2H), 7.28 (m, 2H). ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 148.9, 147.7, 143.8, 136.0, 135.2, 127.3 (2C), 124.2 (2C), 123.5, 122.2, 119.4, 111.7. GLC analysis showed that **6f** had chemical purity higher than 92%.

4.3. Procedure for the preparation of 2-aryl-1-phenyl-1*H*-imidazoles 8 from 1-phenyl-1*H*-imidazole (4a) and aryl bromides 9

Compound **4a** (144 mg, 1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), CuI (0.38 g, 2.0 mmol), sodium or potassium iodide (4.0 mmol) were placed in the reaction vessel under a stream of argon. The reaction vessel, which was fitted with a silicon septum, a reflux condenser and a magnetic stirrer, was evacuated and back-filled with argon, and the sequence was repeated twice. Deaerated DMF (5 mL) and an aryl bromide **9** (2.0 mmol) were then added successively by syringe under a stream of argon. The resulting mixture was stirred at 140 °C under argon for the period of time reported in Table 2. The degree of completion of the reaction was evaluated by GLC and GLC/MS analysis of a sample of the crude reaction mixture after treatment with a saturated aqueous NH_4Cl solution. After being cooled to room temperature the reaction mixture was worked up using the same procedure employed for the Pd- and Cu-mediated C-2 arylation reactions of compounds **4a–d**, **10a–f** and **11a**,**b** with aryl iodides **7**. This procedure was used to prepare compounds **8b** and **8e** in 57 and 72% yield, respectively (Table 2, entries 4 and 5). It should be noted that, at least in the case of the reaction of **4a** with bromobenzene (**9b**), a higher yield of **8b** was obtained when KI was used in place of NaI (compare entries 3 and 4 of Table 2). However, this procedure proved to be unsuitable for the C-2 arylation of **4a** with 4-bromoanisole (**9c**) (Table 2, entry 6).

4.3.1. 1-Phenyl-2[(4-trifluoromethyl)phenyl]-1*H*-imidazole (8e). The crude reaction product obtained in entry 5 of Table 2 by Pd- and Cu-mediated reaction of **4a** with 4-bromobenzotrifluoride (**9b**) in the presence of KI was purified by MPLC on silica gel with a mixture of AcOEt and toluene (50:50+0.1% Et_3N) and subsequent treatment with 3-(mercaptopropyl)-functionalized silica gel to give **8e** (0.21 g, 72%) as a pale yellow solid. Mp 85–87 °C (lit.[11a] mp 85–87 °C). EIMS, *m/z* 289 (15), 288 (92), 287 (100), 269 (6), 261 (22). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 4H), 7.46 (m, 3H), 7.32 (br s, 1H), 7.22 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.0, 138.0, 133.1, 130.4, 129.8 (2C), 128.9 (2C), 128.7 (2C), 125.9 (2C), 125.2 (2C), 124.0, 123.7. The spectral properties of this compound, which had chemical purity higher than 98%, were in agreement with those previously reported.[11a]

4.4. Preparation of 2-(4-aminophenyl)benzothiazole (6c) by selective reduction of 2-(4-nitrophenyl)-benzothiazole (6d)

A suspension of compound **6d** (128 mg, 0.5 mmol) and zinc dust (65.4 mg, 1.0 mmol) in methanol (1 mL) was stirred at room temperature under argon atmosphere with hydrazinium monoformate (0.2 mL), which was prepared by neutralizing slowly equal molar amounts of hydrazine hydrate and 85% formic acid in an ice water bath, with constant stirring. After 44 h at room temperature, the reaction, which initially was exothermic and effervescent, was complete. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The solid residue was recrystallized from EtOH and water to give **6c** (76 mg, 67%) as a colourless solid. Mp 151–153 °C (lit.[49] 155–157 °C). EIMS, *m/z* 228 (6), 227 (16), 226 (100), 113 (6), 108 (8). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, J=7.8 Hz, 1H), 7.89 (m, 2H), 7.84 (d, J=8.1 Hz, 1H), 7.44 (t, J=6.9 Hz, 1H), 7.31 (t, J=6.9 Hz, 1H), 6.72 (m, 2H), 3.83 (br s, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 168.5, 154.2, 149.3, 134.5, 129.2 (2C), 126.1, 124.5, 123.9,

122.5, 121.4, 114.8 (2C). The ^{1}H NMR data of this chemically pure compound were in agreement with those previously reported.[50]

4.5. Preparation of 2-(4-aminophenyl)-1*H*-benzimidazole (6a) by selective reduction of 2-(4-nitrophenyl)-1*H*-benzimidazole (6f)

Compound **6f** (239 mg, 1.0 mmol) was reduced to **6a** (188 mg, 90%) using the same procedure employed for the preparation of **6c** from **6d**. Compound **6a**, which was recrystallized from MeOH and water, was a pale yellow solid. Mp 240–241 °C (lit.[51a] mp 243–244 °C). EIMS, *m*/*z* 210 (15), 209 (100), 208 (15) 181 (6), 104 (9). ^{1}H NMR (300 MHz, CD_3OD) δ 8.51 (br s, 2H), 7.83 (m, 2H), 7.57 (m, 2H), 7.28 (m, 2H), 6.79 (m, 2H). ^{13}C NMR (50.3 MHz, CD_3OD) δ 153.6, 153.3, 137.5 (2C), 129.7 (2C), 124.5 (2C), 115.9, 115.6 (2C), 114.8 (2C). The ^{1}H NMR data of this chemically pure compound were in agreement with those previously reported.[51b]

4.6. General procedure for the Pd/C–CuI mediated C-2 arylation of azoles 4a, 10d and 10f with aryl iodide 7a

A Schlenk-type glass reactor equipped with a silicon septum, a reflux condenser and a magnetic stirrer was evacuated and refilled with argon. The reactor was then charged with an azole (1.0 mmol), 10% Pd/C (53.2 mg, 5 mol%), CuI (0.38 g, 2.0 mmol), aryl iodide **7a** (468 mg, 2.0 mmol) under a stream of argon. Deaerated DMF (5 mL) was then added by syringe and the resulting mixture was stirred at 140 °C under argon for the period of time reported in Scheme 3. Reaction progress was monitored by GLC. After being cooled to room temperature the reaction mixture was worked using the protocol described in Section 4.2. This procedure was employed to prepare **8a** in 90% yield from **4a**, **12d** in 41% yield from **10d** and **12i** in 62% yield from **10f** (Scheme 3). The chemical purity of compounds **8a**, **12d** and **12i** was higher than 98%. Their physical and spectral properties were in good agreement with those of the same compounds prepared by $Pd(OAc)_2$–CuI mediated arylation reactions.

4.7. General procedure for the $Pd(OAc)_2$–CuI-mediated synthesis of 2-aryl-1*H*-indoles 14

Indole (**13a**) (0.12 g, 1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), CuI (0.38 g, 2.0 mmol) and an aryl iodide **7** (2.0 mmol) were placed in the reaction vessel under a stream of argon. The reaction vessel equipped with a silicon septum, a reflux condenser and a magnetic stirrer was evacuated and back-filled with argon, and this sequence was repeated twice. Deaerated DMA (5 mL) was added by syringe under a stream of argon and the mixture was stirred at 160 °C for 48 h. It was then cooled to room temperature and worked up using the protocol reported in Section 4.2. The crude reaction product was purified by MPLC on silica gel. This procedure was employed to prepare 2-aryl-1*H*-indoles **14a**–**c** (entries 2–5, Table 5).

4.7.1. 2-(4-Methoxyphenyl)-1*H*-indole (14a). The crude reaction product obtained in entry 2 of Table 5 by Pd- and Cu-mediated reaction of **13a** with **7a** was purified by MPLC on silica gel with a mixture of toluene and hexane (60:40) as eluent to give **14a** (120 mg, 53%) as a pale yellow solid. Mp 224–227 °C (lit.[53] mp 228–230 °C). EIMS, *m*/*z* 224 (16), 223 (100), 209 (11), 181 (22), 152 (10). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.43 (s, 1H), 7.80 (m, 2H), 7.49 (d, J=7.8 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.03 (m, 4H), 6.76 (d, J=1.7 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 158.7, 137.7, 136.8, 128.8, 126.3 (2C), 124.8, 121.0, 119.6, 119.1, 114.3 (2C), 111.0, 97.2, 55.1. The spectral data of this compound, which had chemical purity higher than 98%, were in agreement with those previously reported.[52]

4.7.2. 2-Phenyl-1*H*-indole (14b). The crude reaction product obtained in entry 4 of Table 5 by Pd- and Cu-mediated reaction of **13a** with **7b** was purified by MPLC on silica gel with a mixture of toluene and hexane (60:40) as eluent to give **14b** (56 mg, 29%) as a colourless solid. Mp 186–188 °C (lit.[54] mp 188–189 °C). EIMS, *m*/*z* 194 (15), 193 (100), 192 (13), 165 (19), 97 (7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.65–7.61 (m, 3H), 7.37 (m, 4H), 7.16 (m, 2H), 6.82 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.9, 136.8, 132.4, 129.3, 129.0 (2C), 127.7, 125.1 (2C), 122.3, 120.7, 120.2, 110.9, 100.0. GLC analysis showed that **14b** had chemical purity higher than 98%. Its spectral properties were in agreement with those previously reported.[55]

4.7.3. 2-[(4-Trifluoromethyl)-phenyl]-1*H*-indole (14c). The crude reaction product obtained in entry 5 of Table 5 by Pd- and Cu-mediated reaction of **13a** with **7d** was purified by MPLC on silica gel with a mixture of toluene and hexane (30:70) as eluent to give **14c** (86 mg, 33%) as a colourless solid. Mp 192–194 °C. EIMS, *m*/*z* 262 (17), 261 (100), 260 (4), 233 (5), 165 (7). ^{1}H NMR (300 MHz, acetone-d_6) δ 7.93 (d, J=7.8 Hz, 2H), 7.63 (d, J=7.8 Hz, 2H), 7.47 (d, J=7.8 Hz, 1H), 7.31 (d, J=8.7 Hz, 1H), 7.02 (t, J=6.9 Hz, 1H), 6.924 (s, 1H), 6.921 (t, J=6.9 Hz, 1H). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 137.3, 135.9, 135.6, 128.2 (q, J_{C-F}=42 Hz), 125.3 (q, J_{C-F}=3.9 Hz, 2C), 124.8 (2C), 123.9 (q, J_{C-F}=226 Hz), 122.1, 120.1, 119.4, 110.84, 110,78, 100.5. Anal. Calcd for $C_{15}H_{10}F_3N$: C, 68.96; H, 3.86. Found: C, 68.83; H, 3.91. GLC analysis showed that **14c** had chemical purity higher than 98%.

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