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Highly selective synthesis of 4(5)-aryl-, 2,4(5)-diaryl-, and 4,5-diaryl-1*H*-imidazoles via Pd-catalyzed direct C-5 arylation of 1-benzyl-1*H*-imidazole

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Abstract

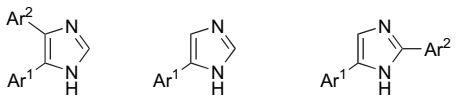
Highly selective, practical, and efficient protocols for the preparation of 4(5)-aryl-1*H*-imidazoles **2**, 2,4(5)-diaryl-1*H*-imidazoles **3**, and 4,5-diaryl-1*H*-imidazoles **1** are described. A key step of these protocols is the regioselective synthesis of 5-aryl-1-benzyl-1*H*-imidazoles **9** by Pd-catalyzed direct C-5 arylation of commercially available 1-benzyl-1*H*-imidazole (**8**) with aryl halides. The three-step synthesis of compounds **3** from **8** also involves the Pd-catalyzed and Cu-mediated direct C-2 arylation of imidazoles **9** with aryl halides under base-free and ligandless conditions. On the other hand, the four-step synthesis of imidazoles **1** from **8** also involves the regioselective bromination of compounds **9** and a Suzuki reaction of the resulting 5-aryl-1-benzyl-4-bromo-1*H*-imidazoles **11** with arylboronic acids **5** under phase-transfer conditions, followed by N-debenzylation.

Keywords: Imidazoles; Direct arylation; Regioselectivity; C–H bond activation; Biologically active compounds

1. Introduction

Mono- and di-*C*-aryl substituted imidazoles are important compounds because of their significant pharmacological and biological activities. Monosubstituted 4(5)-aryl-1*H*-imidazoles, for example, include compounds with good in vitro antifungal activity,[1] potent inhibitors of β-glucosidase,[2] and substances which exhibit activin receptor like kinase 5 (ALK5) inhibitory activity,[3] and several 4(5)-aryl-2-heteroaryl-1*H*-imidazoles have been shown to possess antiinflammatory properties[4] as well as NPY5 receptor antagonist activity.[5] On the other hand, 2-alkyl-4(5)-aryl-1*H*-imidazoles are of interest as potent Na^+ channel blockers[6] and several 5(4)-aryl-4(5)-(4-fluorophenyl)-1*H*-imidazoles are p38 MAP kinase inhibitors.[7] Moreover, 2-*tert*-butyl-4(5)-(4-fluorophenyl)-5(4)-(4-pyridyl)-1*H*-imidazole has been identified as a submicromolar inhibitor of B-Raf,[8] 5(4)-aryl-4(5)-(3,4,5-trimethoxyphenyl)- and 5-aryl-1-methyl-4-(3,4,5-trimethoxyphenyl)-1*H*-imidazoles have been shown to be potent cytotoxic agents able to mimic the activity of combretastatin A-4 against the polymerization of tubulin,[9] and 2-substituted 4,5-diaryl-1*H*-imidazoles have been identified as COX-2 inhibitors[10] and as human CB1 receptor inverse agonists.[11]

In light of this significance, mild and efficient methods for the synthesis of *C*-aryl substituted imidazoles have been developed and a variety of synthetic procedures have been particularly devised for the synthesis of 4,5-diaryl-1*H*-imidazoles **1**.[12] However, despite the progress, the state-of-the-art for the synthesis of these compounds remains less than ideal.



1 **2** **3**

On the other hand, relatively few methods for the synthesis of 4(5)-aryl-1*H*-imidazoles **2** and 2,4(5)-diaryl-1*H*-imidazoles **3** have been reported in the literature and these synthetic

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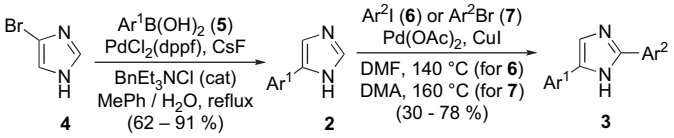
protocols suffer from providing modest yields, requiring unavailable and/or expensive reagents and/or affording significant amounts of byproducts.[13,14] Thus, we thought it right to develop concise and effective novel approaches for the preparation of imidazoles **2** and **3**, and in the context of our studies on the synthesis of arylazole derivatives via highly selective transition metal-catalyzed reactions,[15] we discovered that arylimidazoles **2** can be efficiently and selectively prepared by $PdCl_2$(dppf)-catalyzed Suzuki–Miyaura reaction of cheap and commercially available 4(5)-bromo-1*H*-imidazole (**4**)[16] with arylboronic acids **5** under phase-transfer conditions (Scheme 1).[16] We also established that *N*-unprotected compounds **2** are able to undergo highly selective $Pd(OAc)_2$-catalyzed and CuI-mediated direct C-2 arylation with a variety of activated and inactivated aryl iodides **6** and bromides **7** under base-free and ligandless conditions to produce 2,4(5)diaryl-1*H*-imidazoles **3** in modest to good yields.[16]



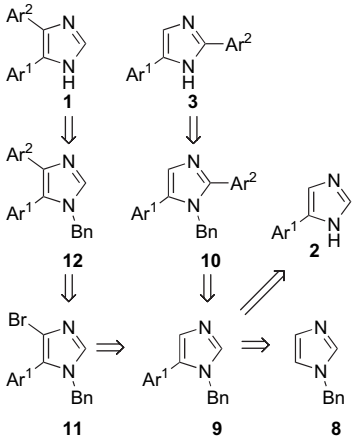
Scheme 1.

In our continuing studies of the Pd-catalyzed intermolecular direct arylation reactions of heteroarenes with aryl halides[17] and their synthetic applications,[15a–d,f,16] we also turned our attention to the preparation of imidazoles **1** and **3** by approaches based on the synthesis of 4(5)-aryl-1*H*-imidazoles **2** via Pd-catalyzed direct C-5 arylation of free (NH)-imidazole with aryl iodides, but, to our disappointment, no expected arylation product was obtained from this reaction using a variety of experimental conditions.[18] However, we were able to develop novel and convenient approaches to the highly selective synthesis of imidazoles **1**–**3** in which the key step was the preparation of 5-aryl-1-benzyl-1*H*-imidazoles **9** by highly selective Pd-catalyzed direct C-5 arylation of commercially available 1-benzyl-1*H*-imidazole (**8**) with a variety of activated and deactivated aryl iodides and bromides. The approach to compounds **3** also involved the Pd-catalyzed and Cu-mediated direct C-2 arylation of imidazoles **9** with aryl iodides **6** or aryl bromides **7** under base-free and ligandless conditions. Herein, we describe the results of these synthetic studies. Scheme 2 outlines the retrosynthetic sequences for the preparation of compounds **1**–**3**. It is worth mentioning that the results of the synthesis of diarylimidazoles **3** from **8** proved to be competitive with those of the two-step procedure summarized in Scheme 1 in which 4(5)-bromoimidazole **4** was used as the starting material.

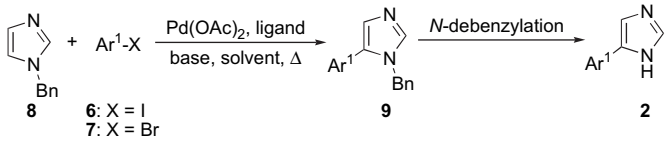
2. Results and discussion

2.1. Synthesis of 4(5)-aryl-1H-imidazoles

Our first goal was the efficient and selective preparation of 4(5)-aryl-1*H*-imidazoles **2**. However, as mentioned in the introduction, several attempts to synthesize these compounds by direct Pd-catalyzed arylation of free (NH)-imidazole with aryl iodides proved to be unsuccessful. We then speculated that, alternatively to the procedure illustrated in Scheme 1, compounds **2** might be conveniently synthesized by the strategy, outlined in the retrosynthetic analysis shown in Scheme 2, which involves the direct C-5 arylation of the *N*-protected imidazole **8** with aryl halides **6** or **7**, followed by deprotection of the resulting 5-aryl-1-benzyl-1*H*-imidazoles **9** (Scheme 3).



Scheme 2.

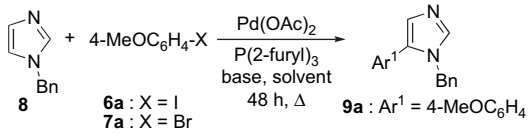


Scheme 3.

No reports on the direct C-5 arylation of **8** have been reported to date. Thus, at the onset of this study we investigated the Pd-catalyzed arylation of this imidazole derivative with two typical unactivated aryl halides, 4-anisyl iodide (**6a**) and 4-anisyl bromide (**7a**). In particular, we evaluated the effect of a number of parameters such as the nature of the halogen of the aryl halide, the base and solvent on the chemical yield, and the selective formation of the required C-5 arylated imidazole **9a**. In fact, two possible regioisomers, i.e., the C-2 and C-4 arylated derivatives **13a** and **14a**, respectively, might also be obtained.

As regards the ligand to be employed in this reaction, we thought it right to use tris(2-furylphosphine) since in a recent study involving the Pd-catalyzed C-5 arylation of 1-methyl-1*H*-imidazole with aryl halides,[19] we found that its use allows the preparation of 5-aryl-1-methyl-1*H*-imidazoles not contaminated by byproducts derived from aryl–aryl scrambling

Table 1
Screening of the reaction conditions for the selective C-5 arylation of **8** with aryl halides **6a** and **7a**

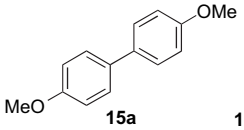


Entry[a]	X	Base	Solvent	Yield of **9a**[b] (%)	C5-selectivity[c]
1	I	CsF	DMF	40	96
2	I	Cs_2CO_3	DMF	46	95
3	I	K_2CO_3	DMF	40	88
4	I	CsF	Toluene	44	88
5	I	Cs_2CO_3	Toluene	37	77
6	I	K_2CO_3	Toluene	—	—
7	I	CsOAc	Toluene	—	—
8	Br	K_2CO_3	DMF	58[d]	100
9	Br	Cs_2CO_3	DMF	51	85
10	Br	KF	DMF	13	93
11	Br	K_2CO_3	Toluene	34	93
12	Br	KF	Toluene	11	90

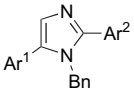
[a] The reactions were run for 48 h with 1 mmol of **8**, 2 mmol of **6a** or **7a**, 5 mol % $Pd(OAc)_2$, and 10 mol % P(2-furyl)$_3$ in 5 mL of solvent at 140 °C (DMF) or at 110 °C (toluene) in the presence of 2 equiv of a base.
[b] The values are referred to GLC yields (naphthalene or biphenyl were used as internal standards). Unless otherwise reported, the values of the conversion were less then 90%.
[c] The C-5 selectivity was expressed as the **9a**/(**9a**+**13a**+**14a**) GLC molar ratio.
[d] Isolated yield. The conversion was quantitative.

reactions involving the ligand and aryl halides.[20] On the other hand, as regards the electrophiles to be employed in the arylation reactions, which we used as a test case, we thought it right to use aryl bromide **7a** in addition to aryl iodide **6a** since aryl bromides are cheaper even though less reactive than the corresponding iodides in some Pd-catalyzed reactions.[21] Moreover, it has been reported that catalyst poisoning occurs in Pd-catalyzed direct intramolecular arylation reactions with aryl iodides due to the accumulation of iodide in the reaction media.[22]

As shown in Table 1, the first experiment was run by reacting imidazole **8** with iodide **6a** under experimental conditions very similar to those used for the selective C-5 arylation of 1-aryl-1*H*-imidazoles.[15a] In particular, **8** was reacted with 2 equiv of **6a** in DMF at 140 °C for 48 h in the presence of 5 mol % $Pd(OAc)_2$, 10 mol % P(2-furyl)$_3$, and 2 equiv of CsF (entry 1, Table 1). After this period of time, the observed C-5 selectivity was 96%, but the GLC yield of **9a** was only 40%. Moreover, GLC and GC–MS analyses showed that the crude reaction mixture was contaminated by significant amount of 4,4′-dimethoxybiphenyl (**15a**) and 4% of the 2,5-diaryl-1*H*-imidazole **10a**.[15f]



15a

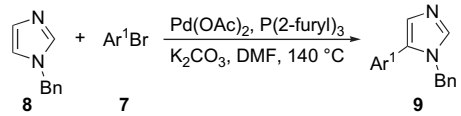


10a : $Ar^1 = Ar^2 = 4\text{-}MeOC_6H_4$

Compound **15a** was presumably derived from a Pd-catalyzed Ullmann-type reductive coupling of **6a**[21] and imidazole **10a** was very likely derived from Pd-catalyzed C-2 arylation of **9a**. Unsatisfactory chemical yields and a lower C-5 selectivity were also observed when the base (entries 2 and 3, Table 1) and solvent (entries 4 and 5, Table 1) were changed. Moreover, no reaction was observed when **8** was reacted with **6a** in toluene in the presence of K_2CO_3 or CsOAc as the base (entries 6 and 7, respectively, Table 1). However, pleasingly, we found that the reaction of **8** with 2 equiv of bromide **7a** in DMF at 140 °C in the presence of 2 equiv of K_2CO_3 occurred in a satisfactory yield and with complete C-5 selectivity (entry 8, Table 1).[23] Interestingly, the crude reaction mixture proved to contain only the expected imidazole **9a** along with ca. 20% of **10a** and a small amount of biphenyl **15a**. By contrast, the use of toluene as the solvent resulted in a diminished yield and 93% C-5 selectivity (entry 11, Table 1), and unsatisfactory results were also obtained when **8** was reacted with **7a** in DMF in the presence of Cs_2CO_3 (entry 9, Table 1) as well as when the reaction of **8** with **7a** was performed in dry DMF or toluene in the presence of KF (entries 10 and 12, respectively, Table 1).

Having successfully demonstrated the viability of the $Pd(OAc)_2$/P(2-furyl)$_3$-catalyzed C-5 arylation of **8** with the deactivated aryl bromide **7a** in DMF in the presence of K_2CO_3 as the base, we then applied the reaction conditions of entry 8 of Table 1 to the synthesis of a number of 5-aryl-1-benzyl-1*H*-imidazoles **9** from **8** and electron-neutral and electron-deficient aryl bromides **7** (Table 2). We found that these arylations showed good to excellent regioselectivity, and occurred in satisfactory to good yields. A satisfactory yield of the required 4(5)-aryl-1*H*-imidazole was also obtained in the Pd-catalyzed reaction of **8** with strongly deactivated bromide **7g** (entry 7, Table 2). We supposed that, analogously to the Pd-catalyzed direct arylations of 1-aryl-1*H*-imidazoles (Ref. 15a) and

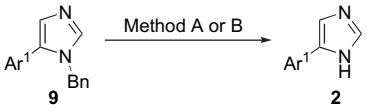
Table 2
Pd-catalyzed regioselective synthesis of 5-aryl-1-benzyl-1*H*-imidazoles **9**



Entry[a]	Ar^1Br		Reaction time (h)	Product		C5-selectivity[c]
	7	Ar^1		**9**	Yield[b] (%)	
1	**7a**	$4\text{-}MeOC_6H_4$	48	**9a**	58	100
2	**7b**	C_6H_5	27	**9b**	73	100
3	**7c**	2-Naphthyl	43	**9c**	72	100
4	**7d**	$4\text{-}ClC_6H_4$	66	**9d**	43	100
5	**7e**	$4\text{-}CF_3C_6H_4$	65	**9e**	45	99
6	**7f**	$4\text{-}MeC_6H_4$	64	**9f**	49	99
7	**7g**	$3,4,5\text{-}(MeO)_3C_6H_2$	70	**9g**	60	100
8	**7h**	6-MeO-2-naphthyl	88	**9h**	66	100
9	**7i**	5-Pyrimidyl	87	**9i**	57	94

[a] The reactions were run with 1 mmol of **8**, 2 mmol of **7**, 5 mol % $Pd(OAc)_2$, and 10 mol % P(2-furyl)$_3$ in 5 mL of DMF at 140 °C in the presence of 2 equiv of K_2CO_3. After the reaction times reported in the table, the reactions were complete.
[b] The values are referred to isolated yields.
[c] The C-5 selectivity is expressed as **9**/(**9**+**13**+**14**) GLC molar ratio.

Table 3
N-Debenzylation of 5-aryl-1-benzyl-1*H*-imidazoles **9** by Pd-catalyzed transfer hydrogenation



Entry	Substrate		Method[a]	Reaction time[b] (h)	Product	
	9	Ar^1			**2**	Yield[b] (%)
1	**9a**	4-$MeOC_6H_4$	A	48	**2a**	97
2	**9c**	2-Naphthyl	A[c]	36	**2c**	57
3[d]	**9b**	C_6H_5	A[e]	144	**2b**	57
4	**9d**	4-ClC_6H_4	A	22	**2b**	(93)[f]
5	**9b**	C_6H_5	B	10	**2b**	99
6	**9f**	4-MeC_6H_4	B	2	**2d**	97
7	**9i**	5-Pyrimidyl	B	2	**2e**	97

[a] *Method A*: 10% Pd/C, 10 equiv of $HCOONH_4$, MeOH, reflux. *Method B*: 20% $Pd(OH)_2$/C, 15 equiv of $HCOONH_4$, MeOH, reflux.
[b] Unless otherwise reported, the reactions were complete after the reported reaction times.
[c] Additional 10 equiv of $HCOONH_4$ were added after 18 h.
[d] A 90% conversion was observed after 144 h.
[e] Aliquots of additional 10 equiv of $HCOONH_4$ were added after 24 and 48 h.
[f] GLC yield.

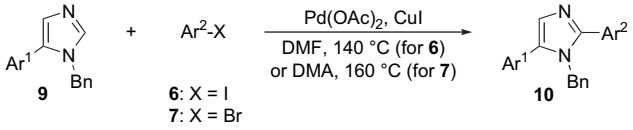
1-methyl-1*H*-imidazole (Ref. 23), a mechanism involving an electrophilic aromatic substitution has to be considered as the most probable for the direct C-5 arylations of compound **8**.

Next, we established the feasibility of *N*-deprotecting compounds **9** by a procedure reported in the literature for the efficient debenzylation of several *N*-benzylamine derivatives,[24a] 1-benzyl-2-methyl-1*H*-imidazole[24b] and 2-amino-1-(5-amino-1-benzyl-1*H*-imidazol-4-yl)ethanone bis(hydrochloride).[24c] Thus, a suspension of a compound **9** and an equal weight of 10% Pd/C in methanol was treated with a large molar excess of anhydrous ammonium formate and the mixture was refluxed for 22–144 h. Entries 1–4 of Table 3 summarize the results obtained in the debenzylation of **9a–9d** according to this procedure (*method A*). Compound **2a** was so obtained in 97% yield after reaction with 10 equiv of ammonium formate for 48 h (entry 1, Table 3). However, as shown in entries 2 and 3 of this table, the N-debenzylation of **9c** and **9b** required the use of overall 20 and 30 equiv of ammonium formate, respectively, and in these cases 10 equiv of the hydrogen transfer reagent were added to the reaction mixtures every 18–24 h.[24d] It is worth noting that use of *method A* for the deprotection of **9d** (entry 4, Table 3) occurred with hydrodehalogenation of the C–Cl bond of this imidazole derivative producing **2b** as the sole reaction product in 93% GLC yield. Notably, reaction times shorter than those of entries 1–4 characterized the N-debenzylation reactions of **9b**, **9f**, and **9i**, which were performed using 15 equiv of ammonium formate in refluxing methanol in the presence of catalytic amounts of Pearlman's reagent (*method B*)[25] (entries 5, 6, and 7, Table 3).

2.2. Synthesis of 2,4(5)-diaryl-1H-imidazoles

According to the retrosynthetic analysis shown in Scheme 2, the synthesis of 2,4(5)-diaryl-1*H*-imidazoles **3** was performed by conversion of compounds **9** into 1-benzyl-2,5-diaryl-1*H*-imidazoles **10** followed by catalytic N-debenzylation. In particular, compounds **10** were prepared by reaction of **9** with 2 equiv of aryl halides **6** or **7** in the presence of 5 mol % $Pd(OAc)_2$ and 2 equiv of CuI under base-free and ligandless conditions (Table 4), using a protocol similar to that we recently developed for the selective direct C-2 arylation of a variety of azoles.[15e,f] These convenient experimental conditions allowed us to avoid the Pd-catalyzed reduction of aryl halides, which can occur when these electrophiles are reacted in the presence of a Pd(II) derivative and an inorganic base in dry DMF at 120–150 °C.[26]

Table 4
Synthesis of 1-benzyl-2,5-diaryl-1*H*-imidazoles **10** by Pd-catalyzed and Cu-mediated direct C-2 arylation of 1-benzylimidazoles **9** with aryl iodides **6** or aryl bromides **7**



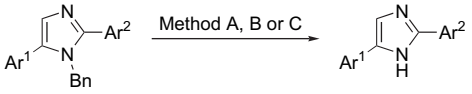
Entry[a]	4(5)-Aryl-1-benzylimidazole		Aryl halide		Reaction time (h)	Product	
	9	Ar^1	**6** or **7**	Ar^2		**10**	Yield (%)
1	**9a**	4-$MeOC_6H_4$	**6b**	C_6H_5	68	**10b**	56
2	**9b**	C_6H_5	**6a**	4-$MeOC_6H_4$	139	**10c**	88
3	**9a**	4-$MeOC_6H_4$	**6a**	4-$MeOC_6H_4$	168	**10a**	21
4	**9b**	C_6H_5	**7c**	2-Naphthyl	65	**10d**	59
5	**9f**	4-MeC_6H_4	**7j**	4-(EtOOC)C_6H_4	140	**10e**	65
6	**9i**	5-Pyrimidyl	**7f**	4-MeC_6H_4	168	**10f**	21

[a] The reactions were run using 1 mmol of **9** and 2 mmol of **6** in 5 mL of DMF at 140 °C or 2 mmol of **7** in 5 mL of DMA at 160 °C in the presence of 5 mol % $Pd(OAc)_2$ and 2 equiv of CuI.

As shown in Table 4, the reactions involving aryl iodides **6** were performed in DMF at 140 °C, but, as expected, those involving aryl bromides **7** required more severe reaction conditions and thus were run in DMA at 160 °C. Notably, a prolonged reaction time was required for all of these reactions, which, nevertheless, occurred with complete C-2 selectivity. Interestingly, the required imidazoles **10b–e** were obtained in satisfactory to good yields (entries 1, 2, 4, and 5, Table 4) but, unexpectedly, compounds **10a** and **10f** were both isolated in 21% yields (entries 3 and 6, respectively, Table 4).

We next turned to the preparation of 2,4(5)-diaryl-1*H*-imidazoles **3** by N-debenzylation of **10**. Table 5 summarizes the results obtained in the deprotection of compounds **10b–e** (entries 1–4). In particular, the clean and efficient debenzylation of **10b** and **10c** was performed according to *method A*, i.e., by refluxing these compounds in methanol in the presence of a catalytic amount of 10% Pd/C and 10 equiv of ammonium formate (entries 1 and 2, respectively, Table 5). In contrast, **3c** was obtained from **10e** in a satisfactory yield using Pearlman's catalyst and ammonium formate as the hydrogen source in refluxing methanol (*method B*) (entry 3, Table 5). This protocol, however, proved to be unsuitable to convert **10d** into **3d** (entry 4, Table 5). Nevertheless, **3d**, which we recently synthesized in 41%

Table 5
N-Debenzylation of 1-benzyl-2,5-diaryl-1*H*-imidazoles **7**



10 **3**

Entry	Reagent			Method[a]	Reaction time (h)	Product	
	10	Ar^1	Ar^2			**3**	Yield[b] (%)
1	**10b**	4-$MeOC_6H_4$	C_6H_5	A	24	**3a**	86
2	**10c**	C_6H_5	4-$MeOC_6H_4$	A	69	**3b**	99
3	**10e**	4-MeC_6H_4	4-(EtOOC)C_6H_4	B	3	**3c**	68
4	**10d**	C_6H_5	2-Naphthyl	B	70	**3d**	—[c]
5	**10d**	C_6H_5	2-Naphthyl	C	70	**3d**	(80)

[a] *Method A*: 10% Pd/C, 10 equiv of $HCOONH_4$, MeOH, reflux. *Method B*: 20% $Pd(OH)_2$/C, 15 equiv of $HCOONH_4$, MeOH, reflux. *Method C*: 20% $Pd(OH)_2$/C, H_2 (1 atm), MeOH, reflux.
[b] Isolated chemical yields. The value in parenthesis is referred to a GLC yield.
[c] Compound **10d** was quantitatively recovered from the reaction mixture.

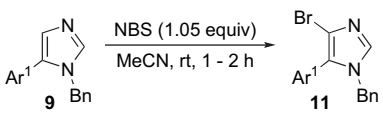
overall yield from bromide **4** according to the two-step reaction sequence illustrated in Scheme 1,[16] could be obtained in 80% GLC yield by debenzylation of **10d** with H_2 at atmospheric pressure (balloon) and $Pd(OH)_2$/C in refluxing methanol (*method C*) (entry 5, Table 5). It should also be noted that the prolonged time of this reaction (70 h) caused the formation of a significant amount of byproduct, which, on the basis of its EIMS spectrum, presumably corresponded to 4(5)-dihydronaphthyl-2-phenyl-1*H*-imidazole.

2.3. Synthesis of 4,5-diaryl-1H-imidazoles

The route followed to prepare 4,5-diaryl-1*H*-imidazoles **1** according to the retrosynthetic strategy illustrated in Scheme 2 is a convergent four-step sequence that relies on the regioselective synthesis of 4-bromoimidazoles **11** by bromination of compounds **9** and a Pd-catalyzed Suzuki–Miyaura reaction between compounds **11** and arylboronic acids **5**, followed by N-debenzylation of the resulting 1-benzyl-4,5-diaryl-1*H*-imidazoles **12**.

It should be noted that this synthetic protocol is significantly different from those previously reported in the literature,[7a] some of which involve the preparation of compounds **1** via multi-step sequences based on the construction of the imidazole ring from commercially unavailable starting reagents.[27]

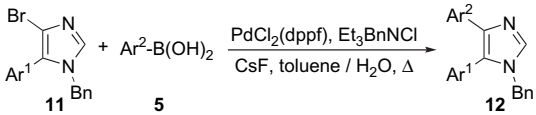
As shown in Scheme 4, compounds **11a–e** were obtained chemically and isomerically pure in 64–80% yield by reaction



9	Ar^1	**11**	Yield (%)
a	4-$MeOC_6H_4$	**a**	80
b	C_6H_5	**b**	80
c	2-naphthyl	**c**	70
e	4-$CF_3C_6H_4$	**d**	79
h	6-MeO-2-naphthyl	**e**	64

Scheme 4.

Table 6
Synthesis of 1-benzyl-4,5-diaryl-1*H*-imidazoles **12** by Pd-catalyzed Suzuki–Miyaura reaction between 4-bromoimidazoles **11** and arylboronic acids **5**



11 **5** **12**

Entry[a]	Reagents				Product	
	11	Ar^1	**5**	Ar^2	**12**	Yield (%)
1	**11a**	4-$MeOC_6H_4$	**5b**	C_6H_5	**12a**	99
2	**11c**	2-Naphthyl	**5c**	3,4,5-$(MeO)_3C_6H_2$	**12b**	92
3	**11c**	2-Naphthyl	**5d**	Benzo[*d*][1,3]dioxol-5-yl	**12c**	93
4	**11d**	4-$CF_3C_6H_4$	**5a**	4-$MeOC_6H_4$	**12d**	67

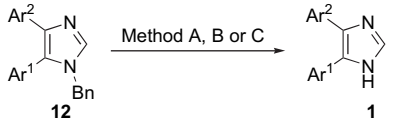
[a] The reactions were run using 1 mmol of **11** and 2 equiv of **5** in 14 mL of a 1:1 mixture of toluene and water at 110 °C (oil bath) for 24 h, in the presence of 5 mol % $PdCl_2$(dppf), 5 mol % Et_3BnNCl, and 3 equiv of CsF.

of the corresponding imidazoles **9a–c**, **9e**, and **9h**, respectively, with a very small molar excess of NBS in MeCN at room temperature.

The first attempts to perform the C-4 arylation of some typical bromoimidazoles **11** involved a Suzuki-type reaction of these bromides with 1.5 equiv of arylboronic acids **5** in a mixture of water and DMF at 100 °C in the presence of 5 mol % $Pd(OAc)_2$, 10 mol % *t*-$Bu_3P\cdot HBF_4$, and 9 equiv of Na_2CO_3.[7a] However, the required 1-benzyl-4,5-diaryl-1*H*-imidazoles **12** were obtained in low to moderate yields.[7a] Moreover, the crude reaction mixtures proved to contain significant amounts of compounds **9** derived from a reductive dehalogenation of bromoimidazoles **11**. However, we were pleased to find that when compounds **11** were reacted with 2 equiv of **5** in a 1:1 mixture of toluene and water at 110 °C for 24 h in the presence of 5 mol % $PdCl_2$(dppf), 5 mol % $BnEt_3NCl$, and 3 equiv of CsF, 1-benzyl-4,5-diarylimidazoles **12** were obtained in good to excellent yields. Table 6 summarizes the results obtained in the preparation of **12a–d**.

Finally, cleavage of the *N*-benzyl protecting group of **12a** by treatment with 10% Pd/C and 10 equiv of ammonium

Table 7
N-Debenzylation of 1-benzyl-2,5-diaryl-1*H*-imidazoles **12**



12 **1**

Entry	Reagent			Method[a]	Reaction time (h)	Product	
	9	Ar^1	Ar^2			**1**	Yield (%)
1	**12a**	4-$MeOC_6H_4$	C_6H_5	A	3	**1a**	99
2	**12b**	2-Naphthyl	3,4,5-$(MeO)_3C_6H_2$	A, B or C	—	**1b**	—[b]
3	**12c**	2-Naphthyl	Benzo[*d*][1,3]dioxol-5-yl	C	69	**1c**	46[c]
4	**12d**	4-$CF_3C_6H_4$	4-$MeOC_6H_4$	C	66	**1d**	99

[a] *Method A*: 10% Pd/C, 10 equiv of $HCOONH_4$, MeOH, reflux. *Method B*: 20% $Pd(OH)_2$/C, 15 equiv of $HCOONH_4$, MeOH, reflux. *Method C*: 20% $Pd(OH)_2$/C, H_2 (1 atm), MeOH, reflux.
[b] Compound **12b** was quantitatively recovered from the reaction mixture.
[c] The reaction occurred in 60% GLC conversion.

formate in refluxing methanol (*method A*) gave 4,5-diaryl-1*H*-imidazole **1a** in 99% yield (entry 1, Table 7).

Unfortunately, attempts at removal of the benzyl group of **12b** according to this method as well as by treatment of **12b** with 20% $Pd(OH)_2/C$ and 15 equiv of ammonium formate in refluxing methanol (*method B*) or by reaction with H_2 (1 atm) in the presence of 20% $Pd(OH)_2/C$ (*method C*) were uniformly unsuccessful and **12b** was quantitatively recovered from the reaction mixtures (entry 2, Table 7). Nevertheless, *method C* proved to be suitable to convert **12c** and **12d** into the required 4,5-diaryl-1*H*-imidazoles, **1c** and **1d**, in 46 and 99% yield, respectively (entries 3 and 4, respectively, Table 7).

3. Conclusions

In this study, we have demonstrated that the benzyl group of commercially available 1-benzyl-1*H*-imidazole (**8**) has two important roles. Firstly, it allows the highly regioselective Pd-catalyzed direct C-5 arylation of the imidazole ring of **8** with both electron-neutral and electron-poor aryl bromides. Secondly, it can be selectively removed from 5-aryl-1-benzyl-1*H*-imidazoles **9** allowing the two-step synthesis of 4(5)-aryl-1*H*-imidazoles **2** from **8**.[16] This result is of particular interest since all attempts to prepare compounds **2** by Pd-catalyzed direct C-5 arylation of (NH)-free imidazole with aryl halides have been unsuccessful so far. This practical and versatile method does not require the use of expensive or sensitive reagents and affords overall yields comparable or not much lower than those obtained by the one-step procedure that involves a Suzuki-type reaction of 4(5)-bromo-1*H*-imidazole (**4**) with arylboronic acids **5**.[16] Furthermore, compounds **9** prepared from **8** as precursors to imidazoles **2** have been shown to be useful starting materials for the regioselective synthesis of 2,4(5)-diaryl-1*H*-imidazoles **3** and 4,5-diaryl-1*H*-imidazoles **1**. Notably, the three-step protocol developed for the synthesis of compounds **3** from **8**, which involves the Pd-catalyzed and Cu-mediated C-2 arylation of imidazoles **9** with both aryl iodides or bromides of any electronic properties under base-free and ligandless conditions, exhibits good functional group tolerance and high regioselectivity. Moreover, its overall yields have proven similar to those obtained by the procedure that allows the two-step preparation of **3** via Pd-catalyzed direct C-2 arylation of imidazoles **2**.[16] Finally, we have developed a four-step approach for the highly regioselective synthesis of 4,5-diarylimidazoles **1**, which represents the first effective and versatile procedure reported so far in the literature for the preparation of this biologically important class of heterocycles in which Pd-catalyzed reactions are used as key steps for the functionalization of the imidazole ring.[7a,28] Unfortunately, this approach, which is potentially useful for the highly regioselective synthesis of a series of imidazoles **1** bearing various substituents on their aryl rings, suffers from the occasionally difficult N-debenzylation of 1-benzyl-4,5-diaryl-1*H*-imidazoles **12** either by Pd-catalyzed transfer hydrogenation or catalytic hydrogenolysis with H_2. Studies aimed to overcome this difficulty are in progress. At present, our attention is also turned to elucidate the mechanism of the Pd-catalyzed and Cu-mediated C-2 arylation of 5-aryl-1-benzyl-1*H*-imidazoles **9**.

4. Experimental

4.1. General

Melting points are uncorrected. Merck precoated 60 F_{254} aluminum 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-5 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 (Aldrich silica gel Merk Grade 9385, particle size 0.040–0.063 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-Benzyl-1*H*-imidazole (**8**), aryl iodides **6**, aryl bromides **7**, $P(2\text{-furyl})_3$, $Pd(OAc)_2$, CuI, $PdCl_2$(dppf), 10% Pd/C (Merck), and 20% $Pd(OH)_2/C$ (Aldrich) were commercially available. The following compounds were prepared according to the literature: 2-(2-naphthyl)-4(5)-phenyl-1*H*-imidazole (**3d**)[16] and 1-benzyl-2-(4-methoxyphenyl)-1*H*-imidazole (**13a**).[15f]

4.2. Procedure for the screening of the reaction conditions for the Pd-catalyzed C-5 arylation of 1-benzyl-1H-imidazole (*8*) with 4-anisyl iodide (*6a*) or 4-anisyl bromide (*7a*)

A mixture of compound **8** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $P(2\text{-furyl})_3$ (23.3 mg, 0.1 mmol), 4-methoxyphenyl iodide **6a** or bromide **7a** (2.0 mmol), and a base (2.0 mmol) in toluene or DMF (5 mL) was stirred under argon for 48 h at the temperature reported in Table 1. After being cooled to room temperature, the crude reaction mixture was diluted with CH_2Cl_2, naphthalene or biphenyl was added as internal standard and the resulting mixture was analyzed by GLC and GC–MS. Table 1 summarizes the results of this screening.

4.3. General procedure for the Pd-catalyzed C-5 arylation of 1-benzyl-1H-imidazole (*8*) with aryl bromides *7*

To a flame-dried reaction vessel equipped with a silicon rubber, a reflux condenser and a magnetic stirrer were added compound **8** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $P(2\text{-furyl})_3$ (23.3 mg, 0.1 mmol), an aryl bromide **7** (2.0 mmol), if a solid, and K_2CO_3 (0.28 g, 2.0 mmol). The reaction vessel was evacuated, and back-filled with argon, and this sequence was repeated twice. DMF (5 mL) and an aryl bromide **7**, if

a liquid, were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was stirred under argon at 140 °C for the period of time reported in Table 2. The completion of the reaction and the composition of the reaction mixture were established on the basis of GLC and GLC–MS analyses of a sample of the reaction mixture treated with a saturated NH_4Cl solution and extracted with AcOEt. After being cooled to room temperature, the reaction mixture was diluted with AcOEt (25 mL), poured into a saturated aqueous NH_4Cl solution (100 mL), and extracted with AcOEt (4×25 mL). The organic extract was washed with brine (2×20 mL), dried, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. This procedure was employed to prepare compounds **9a–i** (Table 2). GLC analysis showed that these compounds had chemical purity higher than 98%.

*4.3.1. 1-Benzyl-5-(4-methoxyphenyl)-1H-imidazole (**9a**)*

The crude reaction product obtained in entry 1 of Table 1 by Pd-catalyzed reaction of **8** with bromide **7a** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **9a** (0.13 g, 58%) as a pale yellow solid. Mp 79–81 °C. EIMS, *m/z* 265 (20), 264 (100), 173 (29), 119 (17), 91 (61). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.28 (m, 3H), 7.19 (m, 2H), 7.08 (s, 1H), 7.01 (m, 2H), 6.88 (m, 2H), 5.11 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.5, 138.2, 133.1, 130.3 (2C), 128.8 (2C), 127.8 (2C), 127.7, 126.6 (2C), 121.9, 114.0, 55.2, 48.5. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10. Found: C, 77.14; H, 6.03.

*4.3.2. 1-Benzyl-5-phenyl-1H-imidazole (**9b**)*

The crude reaction product obtained in entry 2 of Table 2 by Pd-catalyzed reaction of **8** with bromide **7b** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (97:3) as eluent to give **9b** (0.17 g, 73%) as a pale yellow solid. Mp 112 °C. EIMS, *m/z* 235 (18), 234 (95), 92 (8), 91 (100), 65 (11). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.33 (m, 8H), 7.15 (s, 1H), 7.01 (m, 2H), 5.15 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.7, 136.8, 129.8, 128.94 (2C), 128.92 (2C), 128.7 (2C), 128.3, 128.1, 127.9, 126.7 (2C), 119.1, 48.8. The spectral properties of this compound were in agreement with those previously reported.[29]

*4.3.3. 1-Benzyl-5-(2-naphthyl)-1H-imidazole (**9c**)*

The crude reaction product obtained in entry 3 of Table 2 by Pd-catalyzed reaction of **8** with bromide **7c** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **9c** (0.14 g, 72%) as a pale yellow solid. Mp 158–160 °C. EIMS, *m/z* 285 (22), 284 (100), 139 (19), 91 (58). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J=8.79 Hz, 2H), 7.73 (m, 2H), 7.64 (s, 1H), 7.49 (m, 2H), 7.41 (dd, J=8.79 and 1.96 Hz, 1H), 7.29 (m, 4H), 7.05 (m, 2H), 5.21 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.9, 136.8, 133.2, 132.7, 128.9 (2C), 128.6, 128.4, 128.04 (2C), 128.02, 127.8, 127.7, 127.0, 126.7 (2C), 126.65, 126.57, 126.47, 48.9. Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67. Found: C, 84.36; H, 5.43.

*4.3.4. 1-Benzyl-5-(4-chlorophenyl)-1H-imidazole (**9d**)*

The crude reaction product obtained in entry 4 of Table 2 by Pd-catalyzed reaction of **8** with bromide **7d** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **9d** (0.11 g, 43%) as a yellow solid. Mp 79–81 °C. EIMS, *m/z* 270 (23), 269 (12), 268 (68), 91 (100), 65 (10). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.30 (m, 5H), 7.20 (m, 2H), 7.15 (s, 1H), 7.00 (m, 2H), 5.14 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.0, 136.5, 134.2, 130.1, 129.0 (2C), 128.9 (2C), 128.6, 128.2, 128.1 (2C), 126.6 (2C), 123.6, 48.8. Anal. Calcd for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.87. Found: C, 71.39; H, 4.80.

*4.3.5. 1-Benzyl-5-[(4-trifluoromethyl)phenyl]-1H-imidazole (**9e**)*

The crude reaction product obtained in entry 5 of Table 2 by Pd-catalyzed reaction of **8** with bromide **7e** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **9e** (0.13 g, 45%) as a yellow solid. Mp 61–63 °C. EIMS, *m/z* 303 (11), 302 (55), 92 (8), 91 (100), 65 (8). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.59 (s, 1H), 7.36 (m, 5H), 7.22 (s, 1H), 7.01 (m, 2H), 5.18 (s, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 139.6, 136.4, 133.4, 132.1, 129.4, 129.1 (2C), 128.9 (2C), 128.2 (2C), 126.5 (2C), 126.0, 125.7, 125.6, 49.0. Anal. Calcd for $C_{17}H_{13}F_3N_2$: C, 67.54; H, 4.33. Found: C, 67.45; H, 4.24.

*4.3.6. 1-Benzyl-5-(4-tolyl)-1H-imidazole (**9f**)*

The crude reaction product obtained in entry 6 of Table 2 by Pd-catalyzed reaction of **8** with bromide **7f** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **9f** (0.12 g, 49%) as a yellow solid. Mp 89–90 °C. EIMS, *m/z* 249 (15), 248 (77), 103 (6), 92 (8), 91 (100). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.29 (m, 3H), 7.17 (m, 4H), 7.12 (s, 1H), 7.01 (m, 2H), 5.14 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.3, 138.1, 136.8, 133.5, 129.4 (2C), 128.9 (2C), 128.8 (2C), 127.9, 127.7, 126.7 (2C), 126.6, 48.7, 21.2. Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49. Found: C, 82.10; H, 6.36.

*4.3.7. 1-Benzyl-5-(3,4,5-trimethoxyphenyl)-1H-imidazole (**9g**)*

The crude reaction product obtained in entry 7 of Table 2 by Pd-catalyzed reaction of **8** with bromide **7g** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (97:3) as eluent to give **9g** (0.19 g, 60%) as an orange oil. EIMS, *m/z* 325 (21), 324 (100), 310 (9), 309 (47), 91 (65). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.32 (m, 3H), 7.14 (s, 1H), 7.05 (m, 2H), 6.41 (s, 2H), 5.18 (s, 2H), 3.84 (s, 3H), 3.65 (s, 6H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 153.2 (2C), 138.7, 138.0, 137.3, 133.5, 129.0 (2C), 127.9, 126.3 (2C), 126.0, 124.9, 106.2 (2C), 60.9, 55.9 (2C), 48.7. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21. Found: C, 70.27; H, 6.18.

*4.3.8. 1-Benzyl-5-(6-methoxy-2-naphthyl)-1H-imidazole (**9h**)*

The crude reaction product obtained in entry 8 of Table 2 by Pd-catalyzed reaction of **8** with bromide **7h** was purified

by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (96:4) as eluent to give **9h** (0.21 g, 66%) as a pale brown solid. Mp 123–125 °C. EIMS, *m/z* 315 (24), 314 (100), 223 (46), 169 (32), 91 (36). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.33 (m, 4H), 7.19 (m, 2H), 7.12 (s, 1H), 7.04 (m, 2H), 5.19 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 158.2, 138.7, 136.9, 134.0, 129.5, 128.9 (2C), 128.6, 128.3, 127.9, 127.8, 127.2, 127.1, 126.7, 126.7 (2C), 126.0, 124.7, 119.4, 105.6, 55.3, 48.8. Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.83; H, 5.77. Found: C, 80.76; H, 5.60.

4.3.9. 5-(1-Benzyl-1H-imidazol-5-yl)pyrimidine (*9i*)

The crude reaction product obtained in entry 9 of Table 2 by Pd-catalyzed reaction of **8** with bromide **7i** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (93:7) as eluent, followed by recrystallization from CH_2Cl_2 and Et_2O, to give **9i** (0.13 g, 57%) as a pale yellow solid. Mp 143–144 °C. EIMS, *m/z* 237 (8), 236 (51), 92 (8), 91 (100), 65 (10). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.63 (s, 2H), 7.81 (s, 1H), 7.31 (m, 4H), 6.99 (m, 2H), 5.21 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.9, 155.9 (2C), 140.5, 135.5, 130.3, 129.3 (2C), 128.5, 126.4 (2C), 126.0, 124.4, 49.3. Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12. Found: C, 71.06; H, 5.09.

4.4. General procedure for the Pd-catalyzed N-debenzylation of 5-aryl-1-benzyl-1H-imidazoles *9* with 10% Pd/C (method A)

This method was used for the selective N-debenzylation reaction of **9a–c** (entries 1–3, Table 3). To a stirred suspension of 5-aryl-1-benzyl-1*H*-imidazole **9** (1 mmol) and an equal weight of 10% Pd/C in methanol (8 mL), anhydrous ammonium formate (0.63 g, 10 mmol) was added in a single portion under argon. The resulting mixture was stirred under reflux and the reaction was monitored by GLC. The reaction for **9a** was complete after 48 h (entry 1, Table 3) and that involving **9c**, which required the addition of a second aliquot of ammonium formate (0.63 g, 10 mmol) after 18 h, was complete after 36 h (entry 2, Table 3). However, N-debenzylation of **9b** according to this method proved to be much more difficult. In fact, it involved the use of a very large molar excess of ammonium formate (1.89 g, 30 mmol), which was added in three portions after every 24 h (entry 3, Table 3). After completion of the reaction, the reaction mixture was cooled at room temperature and the catalyst was removed by filtration through a Celite pad, which was then washed with methanol. The combined filtrates were concentrated under reduced pressure to give the required 4(5)-aryl-1*H*-imidazole **2**.

4.4.1. 4(5)-(4-Methoxyphenyl)-1H-imidazole (*2a*)

The crude reaction product obtained by N-debenzylation of 1-benzylimidazole **9a** (entry 1, Table 3) was worked up using the general procedure reported for this method to give **2a** (0.168 g, 97%) as a yellow solid. Mp 113–115 °C. The ^{1}H and ^{13}C NMR data of this compound were in good agreement with those of an authentic sample of **2a** prepared by Pd-catalyzed Suzuki–Miyaura reaction of 4(5)-bromo-1*H*-imidazole (**4**) with 4-methoxyphenylboronic acid.[16]

4.4.2. 4(5)-Phenyl-1H-imidazole (*2b*)

The crude reaction mixture obtained by N-debenzylation of 1-benzylimidazole **9b** (entry 3, Table 3) was worked up using the general procedure reported for this method to give **2b** (82 mg, 57%) as a colorless solid. Mp 131–132 °C. The ^{1}H and ^{13}C NMR data of this compound were in good agreement with those of an authentic sample of **2b** prepared by Pd-catalyzed Suzuki–Miyaura reaction of 4(5)-bromo-1*H*-imidazole (**4**) with phenylboronic acid.[16] Compound **2b** was also obtained in 99% yield by Pd-catalyzed N-debenzylation of **9b** according to *method B* (entry 5, Table 3) (see below).

4.4.3. 4(5)-(2-Naphthyl)-1H-imidazole (*2c*)

The crude reaction product obtained by N-debenzylation of 1-benzylimidazole **9c** (entry 2, Table 3) was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (95:5) as eluent to give **2c** (0.110 g, 57%) as a brown solid. Mp 165–166 °C. The ^{1}H and ^{13}C NMR data of this compound were in good agreement with those of an authentic sample of **2c** prepared by Pd-catalyzed Suzuki–Miyaura reaction of 4(5)-bromo-1*H*-imidazole (**4**) with 2-naphthylboronic acid.[16]

4.5. General procedure for the Pd-catalyzed N-debenzylation of 5-aryl-1-benzyl-1H-imidazoles *9* with 20% $Pd(OH)_2$/C (method B)

To a stirred suspension of 5-aryl-1-benzyl-1*H*-imidazole **9** (1 mmol) and 20% $Pd(OH)_2$/C (Aldrich) (0.2 g) in methanol (70 mL), anhydrous ammonium formate (0.95 g, 15 mmol) was added in a single portion under argon. The resulting mixture was stirred under reflux for the period of time reported in Table 3. After completion of the reaction, the reaction mixture was cooled at room temperature and the catalyst was removed by filtration through a Celite pad, which was then washed with methanol. The combined filtrates were concentrated under reduced pressure and the residue was dissolved in AcOEt (50 mL) and washed with a 10% NH_4OH solution. The aqueous phase was extracted with AcOEt (3×15 mL) and the organic extract was washed with brine (2×30 mL) and then concentrated under reduced pressure to give the required 4(5)-aryl-1*H*-imidazole **2**. This method was used for the selective N-debenzylation of **9b**, **9f**, and **9i** (entries 5, 6, and 7, respectively, Table 3).

4.5.1. 4(5)-(4-Tolyl)-1H-imidazole (*2d*)

The crude reaction mixture obtained by N-debenzylation of 1-benzylimidazole **9f** (entry 5, Table 3) was worked up using the general procedure reported for this method to give **2d** (0.153 g, 97%) as a colorless solid. Mp 106–107 °C (lit.[13a] mp 112–114 °C). EIMS, *m/z* 159 (12), 158 (100), 157 (32), 139 (27), 103 (12). ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.39 (br s, 1H), 7.59 (m, 3H), 7.29 (br s, 1H), 7.15 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.0, 136.8, 135.4, 129.9,

129.5 (2C), 124.9 (2C), 115.7, 21.1. Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37. Found: C, 75.83; H, 6.11.

4.5.2. 5-(1H-Imidazol-5-yl)pyrimidine (**2e**)

The crude reaction mixture obtained by N-debenzylation of 1-benzylimidazole **9i** (entry 7, Table 3) was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (90:10) as eluent to give **2e** (0.14 g, 97%) as a colorless solid. Mp 210–213 °C. EIMS, *m/z* 148 (21), 147 (76), 146 (100), 120 (27), 92 (41). ^{1}H NMR (200 MHz, CD_3OD) δ 9.15 (s, 2H), 9.01 (s, 1H), 8.55 (br s, NH), 7.88 (s, 1H), 7.80 (s, 1H). ^{13}C NMR (50.3 MHz, CD_3OD) δ 170.5, 157.0, 154.0 (2C), 138.6, 129.9, 116.9. Anal. Calcd for $C_7H_6N_4$: C, 57.53; H, 4.14. Found: C, 58.03; H, 4.23.

4.6. General procedure for the Pd- and Cu-mediated C-2 arylation of 5-aryl-1-benzyl-1H-imidazoles **9** with aryl halides **6** or **7**

To a flame-dried reaction vessel equipped with a silicon rubber, a reflux condenser, and a magnetic stirrer were added compound **9** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), and CuI (0.38 g, 2.0 mmol). The reaction vessel was evacuated and back-filled with argon and this sequence was repeated twice. A deaerated solution of an aryl iodide **6** (2.0 mmol) in DMF (5 mL) was then added by syringe under a stream of argon and the resulting mixture was stirred under argon at 140 °C for the period of time reported in Table 4. When an aryl bromide **7** (2.0 mmol) was used as the electrophile, the C-2 arylation reaction was performed in DMA (5 mL) at 160 °C for the period of time reported in Table 4. The completion of the reaction was established on the basis of TLC, GLC, and GLC–MS analyses of a sample of the reaction mixture treated with a saturated NH_4Cl solution basified with a few drops of NH_4OH. After being cooled to room temperature, the reaction mixture was diluted with AcOEt (30 mL), poured into a saturated aqueous NH_4Cl solution (100 mL), which was basified with a few drops of NH_4OH, stirred in the open air for 0.5 h, and then extracted with AcOEt (5×25 mL). The organic extract was washed with brine (2×20 mL), dried, and concentrated under reduced pressure and the residue was purified by MPLC on silica gel. This procedure was used to prepare 1-benzyl-2,5-diaryl-1*H*-imidazoles **10a–f** (entries 1–6, Table 4).

4.6.1. 1-Benzyl-5-(4-methoxyphenyl)-2-phenyl-1H-imidazole (**10b**)

The crude reaction product obtained in entry 1 of Table 4 by Pd-catalyzed and Cu-mediated reaction of **9a** with iodide **6b** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **10b** (0.19 g, 56%) as a yellow solid. Mp 107–109 °C. EIMS, *m/z* 341 (14), 340 (53), 281 (11), 249 (100), 207 (88). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.35 (m, 3H), 7.23 (m, 4H), 7.19 (m, 2H), 6.84 (m, 4H), 5.24 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.6, 148.9, 137.9, 134.8, 131.1, 130.5 (2C), 128.7 (4C), 128.5 (2C), 128.7, 127.4, 125.9 (2C), 122.45, 119.1, 114.0 (2C), 55.3, 48.4. Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92. Found: C, 81.03; H, 5.77.

4.6.2. 1-Benzyl-2-(4-methoxyphenyl)-5-phenyl-1H-imidazole (**10c**)

The crude reaction product obtained in entry 2 of Table 4 by Pd-catalyzed and Cu-mediated reaction of **9b** with iodide **6a** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (99:1) as eluent to give **10c** (0.30 g, 88%) as a pale yellow solid. Mp 134–136 °C. EIMS, *m/z* 341 (11), 340 (43), 250 (18), 249 (100), 119 (7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.26 (m, 9H), 6.87 (m, 4H), 5.25 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.1, 149.4, 137.9, 134.8, 130.4, 130.2 (2C), 128.9 (2C), 128.7 (2C), 128.6 (2C), 128.0, 127.9, 127.4, 125.9 (2C), 123.5, 113.9 (2C), 55.3, 48.5. Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92. Found: C, 81.07; H, 5.88.

4.6.3. 1-Benzyl-2,5-di(4-methoxyphenyl)-1H-imidazole (**10a**)

The crude reaction product obtained in entry 3 of Table 4 by Pd-catalyzed and Cu-mediated reaction of **9a** with iodide **6a** was purified by MPLC on silica gel with a mixture of toluene and AcOEt (30:70+0.1% Et_3N) as eluent to give **10a** (78 mg, 21%) as a brown solid. Mp 125–127 °C. EIMS, *m/z* 371 (10), 370 (39), 280 (20), 279 (100), 119 (11). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.56 (m, 6H), 6.85 (m, 6H), 5.21 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 160.0, 159.5, 148.9, 138.0, 134.5, 130.4 (2C), 130.1 (2C), 128.8 (2C), 127.6, 127.4, 125.9 (2C), 123.6, 122.7, 114.0 (2C), 113.9 (2C), 55.3 (2C), 48.3. Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99. Found: C, 78.04; H, 5.81.

4.6.4. 1-Benzyl-2-(2-naphthyl)-5-phenyl-1H-imidazole (**10d**)

The crude reaction product obtained in entry 4 of Table 4 by Pd-catalyzed and Cu-mediated reaction of **9b** with bromide **7c** was purified by MPLC on silica gel with a mixture of toluene and AcOEt (70:30+0.1% Et_3N) as eluent to give **10d** (0.21 g, 59%) as a red solid. Mp 155–157 °C. EIMS, *m/z* 361 (16), 360 (56), 270 (21), 269 (100), 139 (18). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.76 (m, 5H), 7.47 (m, 2H), 7.34 (s, 5H), 7.24 (m, 3H), 6.88 (m, 2H), 5.35 (s, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 149.2, 137.7, 135.4, 133.2, 132.9, 130.0, 129.0 (2C), 128.8 (2C), 128.7 (2C), 128.4, 128.3 (2C), 128.2, 128.0, 127.6, 127.5, 126.7, 126.4, 126.3, 125.9 (2C), 48.7. Anal. Calcd for $C_{26}H_{20}N_2$: C, 86.60; H, 5.59. Found: C, 86.43; H, 5.43.

4.6.5. 1-Benzyl-2-[(4-ethoxycarbonyl)]phenyl-2-(4-tolyl)-1H-imidazole (**10e**)

The crude reaction product obtained in entry 5 of Table 4 by Pd-catalyzed and Cu-mediated reaction of **9f** with bromide **7j** was purified by MPLC on silica gel with a mixture of toluene and AcOEt (70:30+0.1% Et_3N) as eluent to give **10e** (0.26 g, 65%) as a pink solid. Mp 115–117 °C. EIMS, *m/z* 397 (29), 396 (100), 306 (18), 305 (82), 277 (11). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.66 (m, 2H), 7.22 (m, 7H), 7.12 (s, 1H), 6.86 (m, 2H), 5.29 (s, 2H), 4.37 (q, J=7.0 Hz, 2H), 2.34 (s, 3H), 1.38 (t, J=7.0 Hz, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$)

δ 166.2, 147.9, 138.3, 137.5, 136.0, 135.1, 130.4, 129.7 (2C), 129.4 (2C), 129.0 (2C), 128.9 (2C), 128.4 (2C), 127.6, 126.8, 126.0, 125.7 (2C), 61.1, 48.6, 21.2, 14.3. Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10. Found: C, 78.65; H, 5.98.

4.6.6. 5-(1-Benzyl-2-p-tolyl-1H-imidazol-5-yl)-pyrimidine (**10f**)

The crude reaction product obtained in entry 6 of Table 4 by Pd-catalyzed and Cu-mediated reaction of **9i** with bromide **7f** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (97:3) as eluent to give **10f** (68 mg, 21%) as a pink solid. Mp 162–164 °C. EIMS, *m/z* 327 (14), 326 (58), 235 (21), 207 (7), 91 (100). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.61 (s, 2H), 7.49 (m, 2H), 7.39 (s, 1H), 7.24 (m, 5H), 6.86 (m, 2H), 5.27 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 157.7, 155.8 (2C), 151.9, 139.5, 136.7, 130.1, 129.5 (2C), 129.2 (2C), 128.7 (2C), 128.1, 127.2, 125.6 (2C), 125.1, 123.6, 48.9, 21.3. Anal. Calcd for $C_{21}H_{18}N_4$: C, 77.28; H, 5.56. Found: C, 77.16; H, 5.49.

4.7. General methods for the N-debenzylation of 1-benzyl-2,5-diaryl-1H-imidazoles ***10***

Compounds **10b** and **10c** were converted into the corresponding 2,4(5)diaryl-1*H*-imidazoles **3a** and **3b**, respectively, according to the procedure (*method A*) used to prepare imidazoles **2a–c** from 5-aryl-1-benzyl-1*H*-imidazoles **9a–c**. On the other hand, the N-debenzylation reaction of compounds **10d** and **10e** was performed using the same procedure (*method B*) employed for the preparation of imidazoles **2b**, **2d**, and **2e**. However, *method B* proved to be unsuitable for the preparation of **3d** from **10d**. Table 5 summarizes the results obtained in the deprotection of 1-benzyl-2,5-diaryl-1*H*-imidazoles **10b–d**.

4.7.1. 4(5)-(4-Methoxyphenyl)-2-phenyl-1H-imidazole (**3a**)

The crude reaction mixture obtained from the N-debenzylation of **10b** according to *method A* (entry 1, Table 5) was worked up according to the general procedure reported for this method to give **3a** (0.22 g, 86%) as a pale pink solid. Mp 170–174 °C. EIMS, *m/z* 251 (18), 250 (100), 236 (9), 235 (50), 207 (12). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (br s, 1H, NH), 7.86 (m, 2H), 7.65 (m, 2H), 7.30 (m, 3H), 7.22 (s, 1H), 6.89 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 158.9, 146.8, 138.6, 129.8, 128.8 (2C), 128.78, 126.4 (2C), 125.5 (2C), 125.0, 116.6, 114.2 (2C), 55.3. The spectral properties of this compound were in agreement with those previously reported.[30]

4.7.2. 2-(4-Methoxyphenyl)-4(5)-phenyl-1H-imidazole (**3b**)

The crude reaction product obtained by N-debenzylation of 1-benzylimidazole **10c** according to *method A* (entry 1, Table 5) was worked up according to the general procedure reported for this method to give **3b** (0.247 g, 99%) as pale yellow solid. Mp 125–127 °C. The physical and spectral properties of this compound were in good agreement with those previously reported.[15f]

4.7.3. Ethyl 4-(5-p-tolyl-1H-imidazol-2-yl)benzoate (**3c**)

The crude reaction product obtained by N-debenzylation of 1-benzylimidazole **10e** according to *method B* (entry 3, Table 5) was purified by MPLC on silica gel with a mixture of toluene and AcOEt (80:20+0.1% Et_3N) as eluent to give **3c** (0.21 g, 68%) as a colorless solid. Mp 197–198 °C. EIMS, *m/z* 307 (22), 306 (100), 278 (37), 261 (9), 233 (9). ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.11 (m, 4H), 7.79 (m, 3H), 7.22 (m, 2H), 4.34 (q, 2H, *J*=7 Hz), 2.32 (s, 3H), 1.35 (t, 3H, 7 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 165.4, 144.5, 141.9, 135.4, 134.6, 131.6, 129.6 (2C), 129.0 (2C), 128.8, 124.7 (2C), 124.4 (2C), 114.8, 60.7, 20.7, 14.1. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92. Found: C, 75.10; H, 6.03.

4.8. Hydrogenolysis of compound ***10d*** using 20% $Pd(OH)_2$/C (*method C*)

A mixture of **10d** (91 mg, 0.336 mmol) and 20% $Pd(OH)_2$/C (66 mg) in methanol (25 mL) was hydrogenated under an atmospheric pressure of hydrogen using a balloon with vigorous stirring for 70 h under reflux (entry 5, Table 5). The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give a yellow solid residue. TLC, GLC, and GLC–MS analyses showed that it consisted of 2-(2-naphthyl)-4(5)-phenyl-1*H*-imidazole (**3d**) contaminated by ca. 20% of a byproduct, which presumably corresponded to 4(5)-dihydronaphthyl-2-phenyl-1*H*-imidazole. The EIMS data for **3d** were: *m/z* 271 (21), 270 (100), 269 (20), 207 (10), 139 (10). This compound, which was obtained in 80% GLC yield, had GLC retention time and EIMS spectrum identical to those of an authentic sample of **3d** prepared according to the reaction sequence illustrated in Scheme 1.[16]

4.9. General procedure for the synthesis of 5-aryl-1-benzyl-4-bromo-1H-imidazoles ***11***

To a stirred suspension of 5-aryl-1-benzyl-1*H*-imidazole **9** (1 mmol) in anhydrous MeCN (4 mL) was added a solution of freshly recrystallized NBS (0.19 g, 1.05 mmol) in anhydrous MeCN (2 mL) under argon. The resulting solution was stirred at room temperature and the reaction was monitored by GLC and GC–MS. After completion of the reaction (1–2 h), the reaction mixture was diluted with CH_2Cl_2 and the solvents were eliminated at reduced pressure. The crude reaction mixture was purified by MPLC. This procedure was used to prepare bromoimidazoles **11a–e**. GLC analyses showed that these compounds had chemical purity higher than 98%.

4.9.1. 1-Benzyl-4-bromo-5-(4-methoxyphenyl)-1H-imidazole (**11a**)

The crude reaction product obtained by reaction of NBS with 5-arylimidazole **9a** was purified by MPLC on silica gel with a mixture of toluene and AcOEt (80:20) as eluent to give **11a** (0.25 g, 80%) as an orange oil. EIMS, *m/z* 345 (16), 344 (82), 343 (17), 342 (85), 91 (100). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.28 (m, 3H), 7.19 (m, 2H), 6.98 (m, 2H), 6.93 (m, 2H), 5.00 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.0, 136.7,

135.9, 131.6 (2C), 130.1, 128.9 (2C), 128.2, 126.9 (2C), 120.1, 114.9, 114.2 (2C), 55.3, 49.7. Anal. Calcd for $C_{17}H_{15}BrN_2O$: C, 59.49; H, 4.41. Found: C, 59.72; H, 4.69.

4.9.2. 1-Benzyl-4-bromo-5-phenyl-1H-imidazole (**11b**)

The crude reaction product obtained by reaction of NBS with 5-arylimidazole **9b** was purified by MPLC on silica gel with a mixture of toluene and AcOEt (80:20) as eluent to give **11b** (0.27 g, 80%) as a yellow solid. Mp 115–118 °C. EIMS, *m/z* 315 (10), 314 (52), 313 (10), 312 (54), 91 (100). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.40 (m, 3H), 7.29 (m, 5H), 6.97 (m, 2H), 5.04 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.0, 135.8, 130.3 (2C), 128.9 (2C), 128.89, 128.7 (2C), 128.2, 128.1, 127.0 (2C), 119.1, 115.0, 49.9. Anal. Calcd for $C_{16}H_{13}BrN_2$: C, 61.36; H, 4.18. Found: C, 60.98; H, 4.23.

4.9.3. 1-Benzyl-4-bromo-5-(naphthalen-2-yl)-1H-imidazole (**11c**)

The crude reaction product obtained by reaction of NBS with 5-arylimidazole **9c** was purified by MPLC on silica gel with a mixture of toluene and AcOEt (70:30) as eluent to give **11c** (0.25 g, 70%) as a colorless solid. Mp 123–126 °C (CH_2Cl_2). EIMS, *m/z* 365 (11), 364 (51), 363 (12), 362 (52), 91 (100). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.86 (s, 1H), 7.77 (m, 2H), 7.53 (m, 3H), 7.38 (dd, 1H, J=2.1 and 8.7 Hz), 7.29 (m, 3H), 7.00 (m, 2H), 5.09 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.8, 137.1, 135.8, 133.1, 133.0, 130.0, 128.9 (2C), 128.4, 128.3, 128.2, 127.8, 127.3, 127.0 (2C), 126.9, 126.6, 125.4, 115.3, 50.0. Anal. Calcd for $C_{20}H_{15}BrN_2$: C, 66.13; H, 4.16. Found: C, 66.37; H, 4.34.

4.9.4. 1-Benzyl-4-bromo-5-(4-(trifluoromethyl)phenyl)-1H-imidazole (**11d**)

The crude reaction product obtained by reaction of NBS with 5-arylimidazole **9e** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **11d** (0.30 g, 79%) as a yellow oil. EIMS, *m/z* 383 (9), 382 (48), 381 (10), 380 (50), 91 (100). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.59 (s, 1H), 7.43 (m, 2H), 7.31 (m, 3H), 6.99 (m, 2H), 5.09 (s, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 137.9, 135.3, 131.8, 131.2, 130.6 (2C), 129.1 (2C), 128.5 (2C), 128.2, 128.0, 126.9 (2C), 126.6, 126.1, 126.0, 125.7 (q, 1C, J=3.8 Hz), 115.7, 50.2. Anal. Calcd for $C_{17}H_{12}BrF_3N_2$: C, 53.56; H, 3.17. Found: C, 53.85; H, 3.26.

4.9.5. 1-Benzyl-4-bromo-5-(6-methoxynaphthalen-2-yl)-1H-imidazole (**11e**)

The crude reaction product obtained by reaction of NBS with 5-arylimidazole **9h** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (99:1) as eluent to give **11e** (0.25 g, 64%) as a yellow oil. EIMS, *m/z* 395 (23), 394 (94), 393 (24), 392 (100), 91 (86). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.71 (m, 3H), 7.55 (s, 1H), 7.31 (m, 4H), 7.17 (m, 2H), 6.99 (m, 2H), 5.07 (s, 2H), 3.93 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 158.5, 136.9, 135.9, 134.5, 129.8, 129.7, 128.9 (2C), 128.5, 128.2, 127.9, 127.2, 127.0 (2C), 125.4, 123.0, 119.5, 115.1, 105.7, 55.4, 49.9. Anal. Calcd for $C_{21}H_{17}BrN_2O$: C, 64.13; H, 4.36. Found: C, 64.61; H, 4.47.

4.10. General procedure for the synthesis of 4,5-diaryl-1-benzyl-1H-imidazoles **12a–d**

A deaerated mixture of 5-aryl-1-benzyl-4-bromo-1*H*-imidazole **11** (1.0 mmol), arylboronic acid **5** (2.0 mmol), CsF (0.456 g, 3.0 mmol), $PdCl_2$(dppf) (0.041 g, 0.05 mmol), and $BnEt_3NCl$ (0.011 g, 0.05 mmol) in toluene (7 mL) and water (7 mL) was refluxed under argon. After completion of the reaction (24 h), the mixture was cooled to room temperature and partitioned between water and AcOEt, and the organic extract was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel to provide the desired product. This procedure was used to prepare compounds **12a**, **12b**, **12c**, and **12d**.

4.10.1. 1-Benzyl-5-(4-methoxyphenyl)-4-phenyl-1H-imidazole (**12a**)

The crude reaction product obtained by reaction of bromoimidazole **11a** with phenylboronic acid **5b** was purified by MPLC on silica gel with a mixture of toluene and AcOEt (30:70) as eluent to give **12a** (0.34 g, 99%) as a pale orange solid. Mp 144–147 °C. EIMS, *m/z* 341 (26), 340 (100), 249 (19), 119 (20), 91 (32). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.52 (m, 2H), 7.19 (m, 8H), 6.99 (m, 2H), 6.89 (m, 2H), 4.96 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.9, 137.9, 136.8, 136.6, 134.4, 132.2 (2C), 128.8 (2C), 128.1 (2C), 127.9, 126.9 (2C), 126.4 (2C), 126.3, 126.0, 122.3, 114.4 (2C), 55.2, 48.7. Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92. Found: C, 81.63; H, 6.01.

4.10.2. 1-Benzyl-5-(naphthalen-2-yl)-4-(3,4,5-trimethoxyphenyl)-1H-imidazole (**12b**)

The crude reaction product obtained by reaction of bromoimidazole **11c** with 3,4,5-trimethoxyphenylboronic acid **5c** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **12b** (0.42 g, 92%) as an orange solid. Mp 134–135 °C. EIMS, *m/z* 451 (32), 450 (100), 436 (22), 435 (73), 91 (65). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.84 (s, 1H), 7.73 (m, 3H), 7.52 (m, 2H), 7.29 (m, 4H), 6.97 (m, 2H), 6.78 (s, 2H), 5.02 (s, 2H), 3.77 (s, 3H), 3.48 (s, 6H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 152.9, 138.2, 137.0, 136.6, 136.5, 133.2, 133.0, 130.6, 129.8, 128.9, 128.8 (2C), 128.4, 128.0 (2C), 127.9, 127.7, 126.96, 126.93 (2C), 126.8, 126.6, 126.0, 103.3 (2C), 60.8, 55.6 (2C), 48.9. Anal. Calcd for $C_{29}H_{26}N_2O_3$: C, 77.13; H, 5.82. Found: C, 77.54; H, 5.75.

4.10.3. 4-(Benzo[d][1,3]dioxol-5-yl)-1-benzyl-5-(naphthalen-2-yl)-1H-imidazole (**12c**)

The crude reaction product obtained by reaction of bromoimidazole **11c** with benzo[*d*][1,3]dioxol-5-ylboronic acid **5d** was purified by MPLC on silica gel with a mixture of toluene and AcOEt (50:50+0.1% Et_3N) as eluent to give **12c** (0.38 g, 93%) as a colorless solid. Mp 83–85 °C. EIMS, *m/z* 405 (31), 404 (100), 313 (13), 255 (15), 91 (25). ^{1}H NMR (200 MHz,

$CDCl_3$) δ 7.83 (m, 2H), 7.71 (m, 3H), 7.51 (m, 2H), 7.27 (m, 4H), 6.98 (m, 4H), 6.61 (d, 1H, J=8 Hz), 5.84 (s, 2H), 4.98 (s, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 147.4, 146.2, 138.3, 137.1, 136.6, 133.3, 133.1, 130.3 (2C), 128.8 (2C), 128.7, 128.4, 128.2, 128.0, 127.9, 127.0 (2C), 126.8, 126.5, 126.0, 120.4 (2C), 108.2, 107.4, 100.7, 48.9. Anal. Calcd for $C_{27}H_{20}N_2O_2$: C, 80.18; H, 4.98. Found: C, 80.67; H, 5.06.

*4.10.4. 1-Benzyl-4-(4-methoxyphenyl)-5-(4-(trifluoromethyl)-phenyl)-1H-imidazole (**12d**)*

The crude reaction product obtained by reaction of bromo-imidazole **11d** with 4-methoxyphenylboronic acid **5a** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **12d** (0.27 g, 67%) as a pale brown oil. EIMS, *m/z* 409 (27), 408 (100), 317 (12), 119 (12), 91 (45). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.60 (m, 2H), 7.33 (m, 7H), 6.95 (m, 2H), 6.77 (m, 2H), 4.98 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 158.6, 137.8, 137.6, 136.2, 134.6, 131.3 (2C), 128.9 (2C), 128.1 (2C), 126.8 (2C), 126.6 (2C), 126.3, 126.1, 126.0, 125.8, 114.1, 113.8 (2C), 55.2, 49.0. Anal. Calcd for $C_{24}H_{19}F_3N_2O$: C, 70.58; H, 4.69. Found: C, 71.03; H, 4.81.

*4.11. General methods for the N-debenzylation of 1-benzyl-4,5-diaryl-1H-imidazoles **12***

Compounds **12a** was converted into the corresponding 2,4(5)diaryl-1*H*-imidazole **1a** according to the procedure (*method A*) used to prepare imidazoles **2a–c** from 5-aryl-1-benzyl-1*H*-imidazoles **9a–c** (entry 1, Table 7). On the other hand, the N-debenzylation reaction of compounds **12c** and **12d** was performed using the same procedure (*method C*) employed for the preparation of imidazole **3d** (entries 3 and 4, respectively, Table 7). However, *methods A*, *B*, and *C* proved to be unsuitable for the preparation of **1b** from **12b** (entry 2, Table 7).

*4.11.1. 5-(4-Methoxyphenyl)-4-phenyl-1H-imidazole (**1a**)*

Colorless solid (0.25 g, 99%). Mp 193–196 °C. EIMS, *m/z* 251 (24), 250 (100), 249 (36), 235 (20), 206 (14). ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.4 (br s, 1H), 7.78 (s, 1H), 7.51 (m, 2H), 7.42 (m, 5H), 6.97 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 158.3, 135.1, 131.3, 128.8 (2C), 128.2 (2C), 127.9, 127.1 (2C), 126.5, 125.7, 120.4, 113.8 (2C), 55.0. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64. Found: C, 77.24; H, 5.59.

*4.11.2. 4-(Benzo[d][1,3]dioxol-5-yl)-5-(naphthalen-2-yl)-1H-imidazole (**1c**)*

The crude reaction product obtained by N-debenzylation of 1-benzylimidazole **12c** according to *method C* was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (95:5) as eluent to give **1c** (0.15 g, 46%) as a pale orange oil. EIMS, *m/z* 315 (22), 314 (100), 313 (54), 255 (16), 128 (13). ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.86 (m, 4H), 7.53 (m, 3H), 6.94 (m, 3H), 6.09 (s, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 147.2, 146.3, 135.4, 133.0, 131.8, 131.0, 127.7 (2C), 127.6, 127.5, 127.3, 126.2 (2C), 126.0, 125.8, 125.6, 121.2, 108.3, 108.0, 101.0. Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49. Found: C, 77.01; H, 4.52.

*4.11.3. 4-(4-Methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)-1H-imidazole (**1d**)*

Colorless solid (0.32 g, 99%). Mp 59–62 °C. EIMS, *m/z* 319 (19), 318 (100), 317 (27), 303 (19), 205 (10). ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.77 (s, 1H), 7.59 (m, 4H), 7.32 (m, 2H), 6.93 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 161.2, 139.1, 136.8 (2C), 130.8 (2C), 130.0, 129.4, 128.9 (2C), 128.5, 128.4, 126.3 (q, J=4.22 Hz), 125.3, 115.4 (2C), 55.8. Anal. Calcd for $C_{17}H_{13}F_3N_2O$: C, 64.15; H, 4.12. Found: C, 64.76; H, 4.32.

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