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Regioselective Synthesis of 4,5-Diaryl-1-methyl-1*H*-imidazoles Including Highly Cytotoxic Derivatives by Pd-Catalyzed Direct C-5 Arylation of 1-Methyl-1*H*-imidazole with Aryl Bromides

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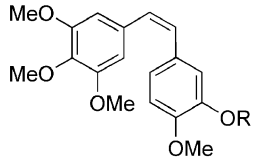
A general and efficient three-step procedure for the highly regioselective synthesis of 1-methyl-1*H*-imidazoles possessing electron-rich, electron-neutral, and/or electron-deficient aryl moieties at their 4- and 5-positions is described. The first step involves the Pd-catalyzed direct C-5 arylation of commercially available 1-methyl-1*H*-imidazole with aryl bromides, and the second and third steps of the sequence involve the selective C-4 bromination of the resulting 5-aryl-1-methyl-1*H*-imidazoles with NBS, followed by a $PdCl_2$(dppf)-catalyzed Suzuki-type reaction between 5-aryl-4-bromo-1-methyl-1*H*-imidazoles and arylboronic acids under phase-transfer conditions. Two 4,5-diaryl-1-methyl-1*H*-imidazoles so prepared, which can be regarded as *Z*-restricted analogues of naturally occurring combretastatin A-4 (CA-4), proved to be highly cytotoxic against a variety of human tumor cell lines, and one of these derivatives has been shown to be more cytotoxic than CA-4 and all of the imidazole derivatives investigated in the literature thus far.

Introduction

Microtubules are polymers of tubulin α,β-dimers that are essential in all eukaryotic cells. Their importance in mitosis makes microtubules an important target for anticancer drugs.[1] Natural products, as well as synthetic, low-molecular-weight compounds of varied structure have been shown to inhibit tubulin polymerization through an interaction with tubulin at different binding sites. The taxol, *Vinca* alkaloid, and colchicine sites are the best known among them.[2] Among all the colchicine-site agents, combretastatin A-4 (CA-4, **1**), isolated from the South African tree *Combretum caffrum*,[3] has received special attention recently.[4] In addition to potent inhibitory activity on tubulin polymerization, CA-4 displays potent cytotoxic activity against a broad spectrum of human cancer cell lines, including multidrug-resistant cells.[3,5] The more water-soluble prodrug of CA-4, CA-4 disodium phosphate (CA-4P, **2**), has been shown to cause vascular shutdown within 1 h of administration, leading to haemorrhagic necrosis at the core of the tumour, while leaving viable tumour cells at the periphery that can cause rapid tumour regrowth.[6] The encouraging antivascular activity of **2** and the potent cytotoxicity of **1** have stimulated the synthesis of numerous analogues of the latter compound in order to have a better understanding of its structure-activity relationships and to enhance both its cytotoxic and selective vascular targeting activity.[4,7,8]



1: R = H
2: R = PO_3Na_2

To overcome the problem of stereomutation of the *Z*-configuration of **1**, which is important for optimal cytotoxic activity, many CA-4 analogues have been developed with a locked *cis*-type bridge between the two aryl groups identical or similar to those of **1**. This result has frequently been achieved by the introduction of a four- or five-membered, heterocyclic, ring system between two vicinal aryl moieties.[8a,8d–8h,8j] As far as the imidazole derivatives are concerned, it should be noted that in 2002, Wang and coworkers[8j] reported that among a small series of 5-aryl-1-(3,4,5-trimethoxyphenyl)-1*H*-imidazoles, **3a** and **3b** had significant antitubulin activity and antiproliferative properties against two lines of human cancer cells.

In the context of our studies on the synthesis and evaluation of the cytotoxic activity of vicinal diaryl-substituted five-membered-ring heterocycles, which can be considered *Z*-restricted analogues of **1**,[9] we also thought it right to investigate the synthesis and bioactivity of vicinal diaryl-substituted imidazoles. In fact, in case of bioactivity prob-

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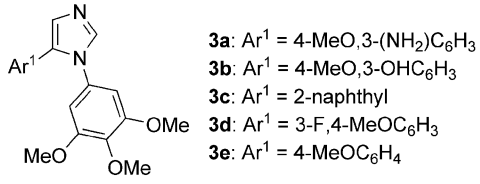
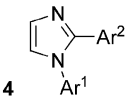
lems associated with the poor solubility of these heterocycles in aqueous media, these derivatives can be easily converted into more soluble salts by treatment with organic or inorganic acids. Thus, we developed selective and efficient general procedures for the synthesis of 1,5- and 1,2-diaryl-1*H*-imidazoles of general formula **3**[10] and **4**,[11] respectively, by the direct transition-metal-catalyzed arylation of 1-aryl-1*H*-imidazoles with aryl halides.[12]



3a: Ar^1 = 4-MeO,3-$(NH_2)C_6H_3$
3b: Ar^1 = 4-MeO,3-OHC_6H_3
3c: Ar^1 = 2-naphthyl
3d: Ar^1 = 3-F,4-$MeOC_6H_3$
3e: Ar^1 = 4-$MeOC_6H_4$



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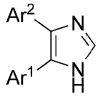

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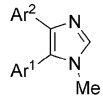
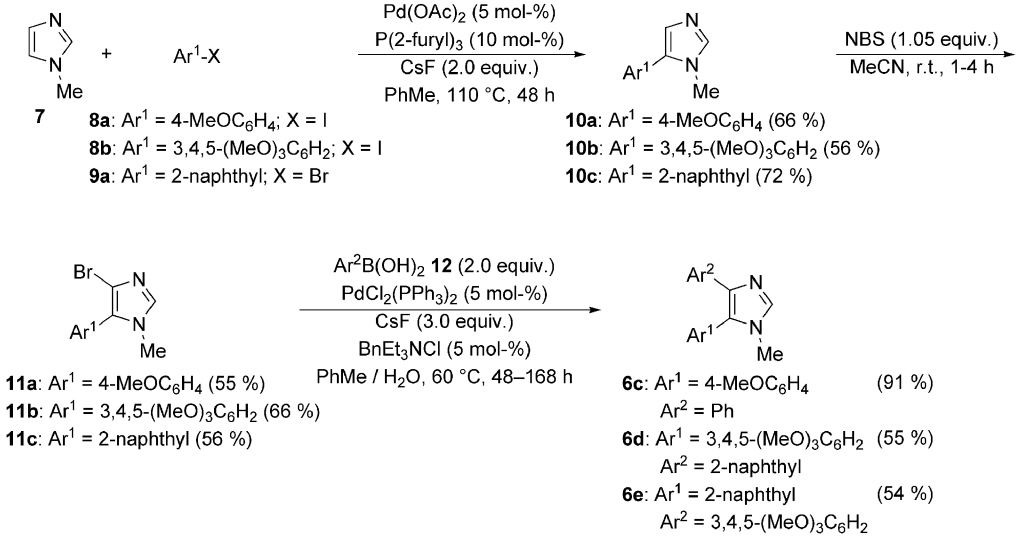
An evaluation of the in vitro antitumor activity of these compounds against the NCI panel of 60 human tumor cell lines indicated that **3c** and **3d** were more cytotoxic than CA-4.[13] It was also observed that imidazoles **3c**–**e** caused profound changes in the morphology of endothelial cells and, following a single treatment, caused massive central necrosis of tumours.[14] More recently, we turned our attention to the synthesis and evaluation of the cytotoxic activity against human tumour cell lines of 4,5-diaryl-1-methyl-1*H*-imidazoles **6**. In fact, Wang and co-workers had previously demonstrated that some 4,5-diaryl-1*H*-imidazoles **5** have cytotoxic and antitubulin activities higher than those of **3** and had shown that the incorporation of an *N*-methyl group into the imidazole ring of **5** can lead to substances, such as **6a** and **6b**, with improved pharmacokinetic properties and excellent bioavailability.[8j] Our interest in the development of a general and efficient protocol for the synthesis of **6** analogs was due to the fact that methods reported in the literature before the beginning of our studies involve the construction of their imidazole ring by multi-step sequences[8j] or are based on a Negishi-type cross-coupling reaction between a haloheteroarene and an imidazol-4-ylzinc reagent, which is not easily available.[15] It was also our aim to identify and prepare 4,5-diaryl-1-methyl-1*H*-imidazoles **6** possessing cytotoxic activity much higher than that of the derivatives described by Wang and co-workers by an inexpensive and environmentally friendly procedure suitable to be scaled up for producing amounts of these heterocycles adequate for biological testing.



6a: Ar^1 = *N*-methylindol-5-yl
Ar^2 = 3,4,5-$(MeO)_3C_6H_2$
6b: Ar^1 = 4-MeO,3-$NH_2C_6H_3$
Ar^2 = 3,4,5-$(MeO)_3C_6H_2$

Our continuing interest in the regioselective synthesis of arylazole derivatives by transition-metal-catalyzed direct arylation[10,11,12a,16] led us to look for a new method for the synthesis of **6** analogs involving the Pd-catalyzed direct arylation of 1-methyl-1*H*-imidazole (**7**) with aryl halides as a key step. Recently, we preliminarily developed such a method and briefly described its use for the synthesis of **6c**–**e** in a review on the synthesis and bioactivity of vicinal diaryl-substituted 1*H*-imidazoles.[17] Scheme 1 summarizes the reaction sequence used to prepare **6c**–**e**. In this paper, we report the experimental details of this three-step procedure. The first step involves the Pd-catalyzed direct C-5 arylation of **7** with aryl iodides **8a** and **8b** and aryl bromide **9a**, followed by the regioselective C-4 bromination of the resulting 5-aryl-1-methyl-1*H*-imidazoles **10a**–**c** by treatment with NBS in the second step. The last step consists of a $PdCl_2(PPh_3)_2$-catalyzed Suzuki-type reaction between 5-aryl-4-bromo-1-methyl-1*H*-imidazoles **11a**–**c** and arylboronic acids **12** with CsF as the base under phase-transfer conditions. Moreover, we describe an improvement of this three-step route, which allowed us to synthesize conveniently, regioselectively, and in high overall yields, a variety



Scheme 1.

of 4,5-diaryl-1-methyl-1*H*-imidazoles characterized by electron-rich, electron-neutral, and/or electron-deficient aryl moieties.

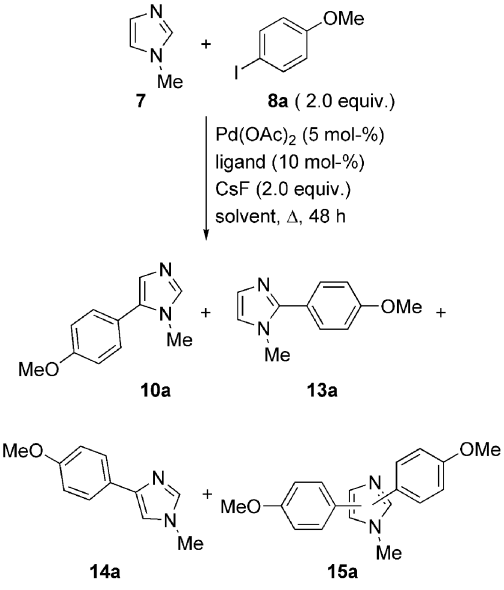
This improved route involves the use of reactions similar to those depicted in Scheme 1. In the first step, a variety of 5-aryl-1-methyl-1*H*-imidazoles **10** were efficiently prepared with significantly higher regioselectivity than that obtained in our preliminary investigation. This was accomplished by a $Pd(OAc)_2$/P(2-furyl)$_3$-catalyzed direct arylation of **7** with deactivated, unactivated, and activated aryl bromides in DMF at 110 °C with K_2CO_3 as the base. Moreover, our modification of the catalyst system in the Suzuki-type reaction between arylboronic acids and 5-aryl-4-bromo-1-methyl-1*H*-imidazoles **11** allowed us to prepare the required 4,5-diaryl-1-methyl-1*H*-imidazoles **6** in shorter reaction times than those shown in Scheme 1 and with comparable or higher isolated yields. Finally, we report that two compounds of general formula **6** were evaluated for their antitumoral activity against the NCI panel of 60 human tumor cell lines and were found to be highly cytotoxic. Remarkably, imidazole **6d** possessed cytotoxic activity higher than that of CA-4 and all of the imidazole derivatives investigated in the literature thus far.

Results and Discussion

Synthesis of 5-Aryl-1-methyl-1*H*-imidazoles

Several methods have been reported in the literature for the synthesis of 5-aryl-1-methyl-1*H*-imidazoles **10**, which in our synthetic plan represent key intermediates. The methods include the CuCl-mediated reaction of aryl nitriles with (methylamino)acetaldehyde dimethyl acetal,[18] the van Leusen chemistry of a tosmic reagent,[8j] the Pd-catalyzed Suzuki reaction of arylboronic acids with 5-bromo-1-methyl-1*H*-imidazole,[19] and the Pd-catalyzed direct C-5 arylation of 1-methyl-1*H*-imidazole (**7**) with aryl halides.[20] The latter methodology offers a number of advantages over the other procedures, including convenience, simplicity, and the use of readily available starting materials, but the different protocols used thus far to perform the direct arylation reaction met with limited success because of modest yields,[20a,b,d] low regioselectivity,[20b,d] and the use of electrophiles represented exclusively by activated aryl halides.[20c] With the aim of overcoming these problems, at the outset of our studies on the synthesis of compounds **10**, we investigated the synthesis of **10a** by reacting **7** with 4-iodoanisole (**8a**) under experimental conditions very similar to those used for the selective C-5 arylation of 1-aryl-1*H*-imidazoles.[10] Thus, **7** was treated with 2 equiv. of **8a** with 5 mol-% $Pd(OAc)_2$, 10 mol-% PPh_3, and 2 equiv. of CsF in DMF at 140 °C for 48 h (Table 1, Entry 1). After this period of time, the arylation had proceeded to 98% conversion and provided a mixture of compounds, which proved to contain monoarylation derivatives **10a**, **13a**, and **14a** and a diarylated 1-methyl-1*H*-imidazole (**15a**), along with very small amounts of monophenyl-substituted 1-methyl-1*H*-imidazoles. The latter compounds presumably derived from undesirable side reactions involving aryl/aryl exchange between Pd- and phosphane-bound phenyl groups.[21] Compound **13a** was identified by comparison of its physical and spectral properties with those of an authentic sample of 2-(4-methoxyphenyl)-1-methyl-1*H*-imidazole, which had been previously synthesized in excellent yield by the Pd-catalyzed and Cu-mediated direct C-2 arylation of **7** with **8a** under ligandless conditions.[11] Compound **10a** was obtained in 50% isolated yield and 64% selectivity. We then attempted to improve the yield and selectivity of the arylation reaction and to minimize the formation of byproducts. Thus, the effects of the ligand and solvent were examined. As far as the selectivity is concerned, we found that when PPh_3 was replaced by $AsPh_3$ (Table 1, Entry 2,) or P(2-furyl)$_3$ (Table 1, Entries 3 and 4), the selectivity increased, and cleaner reaction mixtures were obtained, which did not contain compounds derived from the scrambling of the aryl moiety of **8a** with the organic group of the ligand. We were also pleased to find that switching to toluene as solvent and with a catalyst precursor consisting of a mixture of $Pd(OAc)_2$ and P(2-furyl)$_3$ in a 1:2 mole ratio (Table 1, Entry 4), the reaction produced a significant increase in the yield.

Table 1. Screening reaction conditions for the C-5 arylation of **7** with **8a**.



Entry	Ligand	Solvent	Temp. [°C]	GLC conv. of **7** [%]	**10a/13a/14a/15a** GLC mole ratio	Isolated yield of **10a** [%]
1	PPh_3	DMF	140	98	64:1:3:32	50
2	$AsPh_3$	DMF	140	94	72:1:2:25	50
3	P(2-furyl)$_3$	DMF	140	90	73:2:11:14	36
4	P(2-furyl)$_3$	PhMe	110	94	75:2:1:22	66

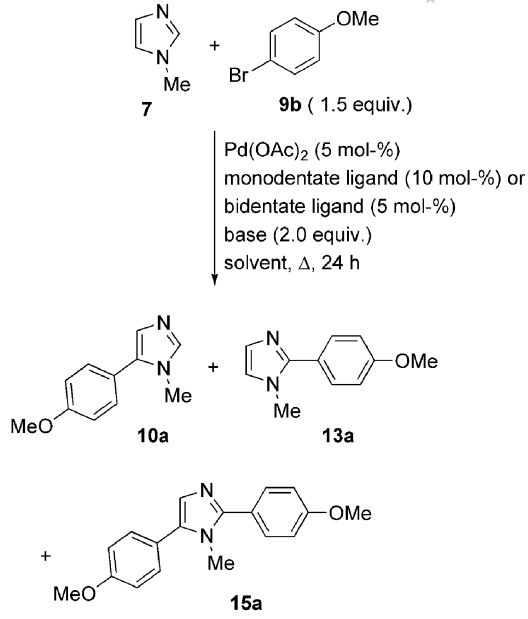
This satisfactory result prompted us to apply the reaction conditions of Entry 4 of Table 1 to the synthesis of 5-aryl-1-methyl-1*H*-imidazoles **10b** and **10c** from **7** and 5-iodo-1,2,3-trimethoxybenzene (**8b**) and 2-bromonaphthalene (**9a**), respectively. In these reactions, we found regioselectiv-

ity very similar to that of the arylation of **7** with **8a** in Entry 4 of Table 1, and as shown in Scheme 1, furnished the required compounds **10b** and **10c** in 56 and 72% yield, respectively.

Since the use of unactivated aryl bromide **9a** in the C-5 arylation of **7** gave better results than those obtained with aryl iodides **8a** and **8b**, we then investigated the Pd-catalyzed direct arylation of **7** with a variety of aryl bromides **9**, including deactivated and activated derivatives. In fact, many aryl bromides **9** are commercially available and less expensive than the corresponding iodides **8**. Moreover, we examined the possibility of decreasing the aryl halide/**7** mole ratio from 2:1 (as in Scheme 1) to 1.5:1. Thus, we began this investigation by examining the effects of variables such as the reaction temperature and the nature of the base, solvent, and phosphane ligand on the outcome of the direct arylation of **7** with 1.5 equiv. of 4-bromoanisole (**9b**), a typical deactivated aryl bromide, with a catalytic amount of $Pd(OAc)_2$ (Scheme 2). A wide range of bases that included K_2CO_3, Cs_2CO_3, KOAc, CsOAc, KF, CsF, and piperidine were tested in the reaction of **7** with **9b**, which we performed in DMF at 110 °C with a mixture of $Pd(OAc)_2$ (5 mol-%) and P(2-furyl)$_3$ (10 mol-%). Reasonable isolated yields (46–49%) of the required arylation product **10a** were obtained only when K_2CO_3 or CsOAc was used; other bases proved to be ineffective in the arylation. However, the highest GLC and isolated yields of **10a** (55 and 49%, respectively) were obtained when K_2CO_3 was employed as the base. In fact, CsOAc afforded somewhat lower selectivity in the reaction (the **10a**/**13a**/**15a** mole ratio was 91:0:9), and **10a** was isolated in 46% yield. Other major factors controlling the regioselectivity of the reaction were found to be the solvent and reaction temperature (Table 2). More polar solvents favoured the desired C-5 arylation, and DMF was the preferred solvent at the preferred temperature of 110 °C (Table 2, Entries 1 and 4).

The use of other polar solvents such as DMA (Table 2, Entry 2) or DMSO (Table 2, Entry 5) produced **10a** in yields comparable to that obtained in DMF at 110 °C, but the selectivity was significantly lower. On the other hand, the use of less polar solvents such as toluene (Table 2, Entry 7) or xylenes (Table 2, Entry 8) resulted in low GLC yields of **10a** and unsatisfactory regioselectivity. The identity of the byproduct **15a** from reactions lacking complete regioselectivity (Table 2, Entries 2, 4, 5, 7 and 8) was confirmed by its isolation and comparison with an authentic sample of 2,5-bis(4-methoxyphenyl)-1-methyl-1*H*-imidazole, synthesized in 22% yield by the Pd-catalyzed bis-arylation reaction of **7** with 2.0 equiv. of **9b**, as depicted in Scheme 3.

The choice of the ligand was also an important factor, with P(2-furyl)$_3$ being preferred over P(c-C_6H_{11})$_3$ or bidentate phosphane ligands such as dppf or Xantphos (Table 3). In fact, the use of 10 mol-% of P(2-furyl)$_3$ in the reaction of **7** with **9b** with 2 equiv. of K_2CO_3 and 5 mol-% $Pd(OAc)_2$ in DMF at 110 °C produced **10a** with regioselectivity and a GLC yield higher than that observed for the same reaction with P(c-C_6H_{11})$_3$ instead of P(2-furyl)$_3$ (compare Table 3, Entries 1 and 3). On the other hand, **10a** was obtained in 39% GLC yield when the reaction of **7** with **9b** was run in DMF with 5 mol-% of Xantphos (Table 3, Entry 4), but the regioselectivity of the reaction was significantly lower than that of the reactions of Entries 1 and 3 of Table 3. It is interesting to note that **10a** was synthesized in 33% GLC yield and 100% regioselectivity when the arylation was performed under ligandless conditions (Table 3,

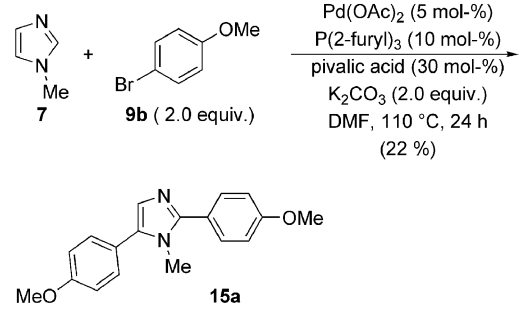


Scheme 2.

Table 2. Solvent and reaction temperature optimization for the $Pd(OAc)_2$/P(2-furyl)$_3$-catalyzed reaction of **7** with **9b**.

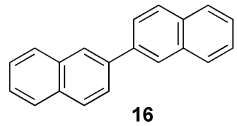
Entry[a]	Solvent	Reaction temp. [°C]	**10a**/**13a**/**15a** mole ratio	GLC yield of **10a** [%][b]
1	DMF	110	100:0:0	55
2	DMA	110	96:4:0	54
3	NMP	110	100:0:0	8
4	DMF	140	63:0:37	44
5	DMSO	140	90:6:4	44
6	MeCN	85	–	–
7	PhMe	110	93:6:1	32
8	$Me_2C_6H_4$	140	10:3:87	9

[a] The reactions were performed with 1 mmol of **7**, 1.5 mmol of **9b**, 5 mol-% $Pd(OAc)_2$, and 10 mol-% P(2-furyl)$_3$ with 2 equiv. of K_2CO_3 for 24 h. [b] Evaluated with biphenyl as an internal standard.



Scheme 3.

Entry 6). Ultimately, the preferred conditions found in the reaction screen were a $Pd(OAc)_2/P(2\text{-furyl})_3$ catalyst system and K_2CO_3 as the base in DMF at 110 °C. With the standard reaction conditions in hand, we then proceeded to test the generality of the reaction with a number of aryl bromides. Entries 1, 2, and 7 of Table 4 show that deactivated aryl bromides, including strongly deactivated bromide **9c**, efficiently participated in the completely regioselective Pd-catalyzed C-5 arylation of **7**. The yields of **10a** and **10b** were slightly lower than those obtained when 2 equiv. of the more expensive aryl iodides **8a** and **8b** were used. The results reported also indicate that both unactivated and activated aryl bromides provided the required 5-aryl-1-methyl-1*H*-imidazoles **10** generally in good yields and with satisfactory to excellent selectivity (Table 4, Entries 3–5, 8, and 10). Nevertheless, a comparison of Entry 3 of Table 4 with Scheme 1 indicates that the protocol for the C-5 arylation of **7** with 1.5 equiv. of **9a** with K_2CO_3 as the base furnished **10c** in a slightly lower yield than that obtained with 2 equiv. of **9a** and CsF as the base (67% vs. 72%) but with complete C-5 regioselectivity and without the formation of significant amounts of 2,2′-binaphthyl (**16**), derived from the homocoupling of **9a**.



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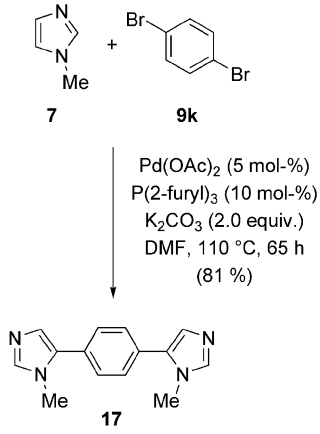
It should also be noted that, unexpectedly, no arylation occurred in the reaction of **7** with methyl 2-bromobenzoate (**9i**, Table 4, Entry 9), and a low yield (24%) of the required arylation product, **10f**, was obtained when the moderately deactivated, sulfur-containing, heteroaryl bromide **9f** was used (Table 4, Entry 6). Interestingly, a modification of the procedure illustrated in Table 4 that involved a large molar excess of **7** with respect to the electrophile produced 1,4-bis(1-methyl-1*H*-imidazol-5-yl)benzene (**17**) in 81% isolated yield from **7** and 1,4-dibromobenzene (**9k**, Scheme 4).



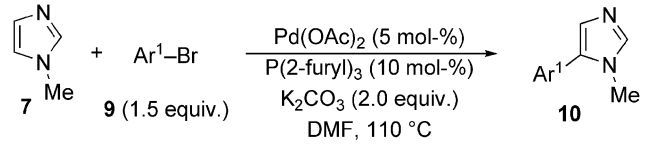
Scheme 4.

Table 3. Ligand optimization for the reaction of **7** with **9b** with K_2CO_3 and a catalytic amount of $Pd(OAc)_2$.

Entry[a]	Ligand	Solvent	**10a/13a/15a** mole ratio	GLC yield of **10a** [%][b]
1	$P(2\text{-furyl})_3$	DMF	100:0:0	55
2	dppf	DMF	100:0:0	9
3	$P(c\text{-}C_6H_{13})_3$	DMF	96:0:4	50
4	Xantphos	DMF	87:2:11	39
5	$P(c\text{-}C_6H_{13})_3$	PhMe	–	–
6	–	DMF	100:0:0	33

[a] The reactions were performed h at 110 °C for 24 with 1 mmol of **7**, 2.0 mmol of **9b**, 5 mol-% $Pd(OAc)_2$, and 10 mol-% of a monodentate ligand or 5 mol-% of a bidentate ligand with 2 equiv. of K_2CO_3. [b] Evaluated with biphenyl as an internal standard.

Table 4. Pd-catalyzed synthesis of 5-aryl-1-methyl-1*H*-imidazoles **10** from 1-methyl-1*H*-imidazole **7** and aryl bromides **9**.



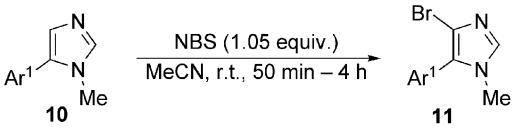
Entry	Aryl bromides Ar^1	**9**	Reaction time [h]	Products **10**	Sel. [%]	Isolated yield [%]
1	4-MeOC_6H_4	**9b**	24	**10a**	100	49
2	$3,4,5\text{-(MeO)}_3C_6H_2$	**9c**	48	**10b**	100	55
3	2-naphthyl	**9a**	48	**10c**	100	67
4	3-pyridyl	**9d**	51	**10d**	100	66
5	$4\text{-CF}_3C_6H_4$	**9e**	48	**10e**	93	74
6	2-*i*Pr-5-thienyl	**9f**	72	**10f**	100	24
7	6-MeO-2-naphthyl	**9g**	90	**10g**	100	70
8	4-ClC_6H_4	**9h**	48	**10h**	80	66
9[a]	2-(MeOOC)C_6H_4	**9i**	48	–	–	–
10	C_6H_5	**9j**	48	**10i**	98	80

[a] The reaction was run in DMA at 160 °C.

Synthesis of 5-Aryl-4-bromo-1-methyl-1*H*-imidazoles

We then investigated the selective C-4 bromination of 5-aryl-1-methyl-1*H*-imidazoles **10**, and we envisaged that this reaction might be efficiently performed with experimental conditions similar to those previously employed to convert both 1,5-diaryl-1*H*-imidazoles and 1-benzyl-5-methyl-1*H*-imidazole into the corresponding 4-halo derivatives.[22,23] To test this hypothesis, we reacted **10i** with 1.05 equiv. of *N*-bromosuccinimide (NBS) in acetonitrile at room temperature and obtained a mixture of 4-bromo derivative **11g** and a small amount (about 3–4%) of 2-bromo derivative **18**. Chromatographic purification of this mixture provided **11g** in 72% yield (Table 5, Entry 1). As reported in the next section, the structural assignment of this compound was confirmed by its conversion into 4,5-diphenyl-1-methyl-1*H*-imidazole (**6f**) by a Suzuki-type reaction with phenylboronic acid and a comparison of the physical and spectral properties of this imidazole derivative with those of an authentic sample of **6f**, prepared by the *N*-methylation of commercially available 4,5-diphenyl-1*H*-imidazole (**5a**) by a reaction with a large molar excess of dimethyl carbonate with K_2CO_3 and 5 mol-% 18-crown-6 (Figure 1).[24]

Table 5. C-4 bromination of 5-aryl-1-methyl-1*H*-imidazoles **10**.



Entry	5-Aryl-1-methyl-1*H*-imidazole		Reaction time	Product	
	10	Ar^1	[h]	**11**	Isolated yield [%]
1	**10i**	C_6H_5	0.83	**11g**	72
2	**10a**	4-$MeOC_6H_4$	1	**11a**	55
3	**10b**	3,4,5-$(MeO)_3C_6H_2$	1	**11b**	72
4	**10c**	2-naphthyl	2	**11c**	58
5	**10d**	3-pyridyl	4	**11d**	71
6	**10g**	6-MeO-2-naphthyl	1	**11e**	72
7	**10h**	4-ClC_6H_4	1	**11f**	76

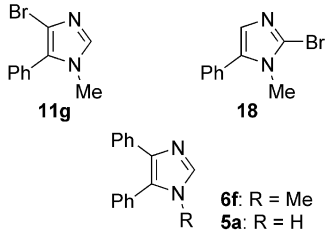


Figure 1. Chemical structures of **11g**, **18**, **6f**, and **5a**.

We then tested the viability of the envisioned protocol for the C-4 bromination of **10i** for the preparation of a variety of 5-aryl-4-bromo-1-methyl-1*H*-imidazoles **11** displaying electron-rich, electron-deficient, or electron-neutral aryl moieties. We found that all the reactions were highly regioselective and provided the required bromo derivatives **11** in short reaction times and good yields. Table 5 summarizes the results obtained in the preparation of **11a**–**g**. Interestingly, the yields of these 4-bromo derivatives did not significantly differ from those recently obtained in the C-4 bromination of 5-aryl-1-benzyl-1*H*-imidazoles with a procedure similar to that illustrated in Table 5.[16c]

Synthesis and Cytotoxicity of 4,5-Diaryl-1-methyl-1*H*-imidazoles

Having secured good access to **11** analogs, we next turned our attention to the conversion of these bromoimidazoles into 4,5-diaryl-1-methyl-1*H*-imidazoles **6** by a Suzuki-type reaction with arylboronic acids **12**. We thought it right to perform the Pd-catalyzed cross-coupling reactions under phase-transfer conditions according to a procedure similar to one we previously employed for the C-4 arylation of 3,4-dichloro-2(5*H*)-furanone[9a] and the synthesis of 4(5)-aryl-1*H*-imidazoles from 4(5)-bromo-1*H*-imidazole.[16d]

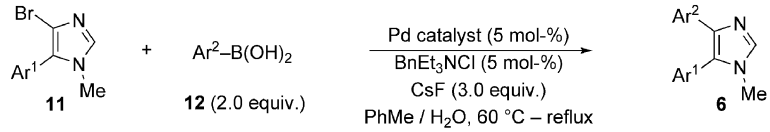
We first attempted the C-4 arylation of bromoimidazoles **11a**, **11b**, and **11c** with 2 equiv. of phenylboronic acid (**12a**), 3,4,5-trimethoxyphenylboronic acid (**12b**), and 2-naphthylboronic acid (**12c**), respectively, in a 1:1 mixture of toluene and water at 60 °C with 5 mol-% $PdCl_2(PPh_3)_2$, 5 mol-% $BnEt_3NCl$, and 3 equiv. of CsF (Method A). As shown in Scheme 1 and Entries 1, 2, and 3 of Table 6, these reactions provided the required products, **6c**, **6e**, and **6d**, in 91, 54, and 55% yield, respectively. Remarkably, the cross-coupling reactions producing **6d** and **6e**, unlike the arylation of 3,4-dichloro-2(5*H*)-furanone[25] and 4(5)-bromo-1*H*-imidazole[16d] under very similar experimental conditions, were not accompanied by an undesirable side reaction of aryl/aryl interchange between Pd- and phosphane-bound phenyl groups. Nevertheless, the arylation of **11c** and **11b** met with limited success, providing modest yields but requiring long reaction times (Table 6, Entries 2 and 3). Therefore, we investigated an alternative procedure for the cross-coupling of bromoimidazoles **11** with arylboronic acids. After extensive experimentation, we found that when $PdCl_2(dppf)$ replaced $PdCl_2(PPh_3)_2$ and the reactions were performed in a refluxing 1:1 mixture of toluene and water with a catalytic amount of $BnEt_3NCl$, the arylation of bromoimidazoles **11b**–**g** (Method B) occurred in good to excellent yields and with a significant reduction in the reaction time compared to those of Method A (Table 6, Entries 4–11). A comparison between Entries 5 and 6 and Entries 2 and 3, respectively, of Table 6 highlights the synthetic advantage of Method B over Method A. The results of Table 6 also indicates that the Suzuki-type reactions performed with Method B allowed us to efficiently introduce electron-neutral, electron-rich, or electron-deficient aryl groups at the 4-position of bromoimidazoles **11**.

Finally, we note that three 4,5-diaryl-1-methyl-1*H*-imidazoles prepared herein (i.e. **6d**, **6e**, and **6j**), which can be regarded as *Z*-restricted analogues of combretastatin-A4, were selected by the NCI for cytotoxic activity testing against the panel of 60 human tumour cell lines. The results for **6j** are nor available yet, but those for **6d** and **6e** indicate that both of these compounds are highly cytotoxic. In fact, the mean molar drug concentration value of Log GI_{50} (MG_MID Log GI_{50}) for all tested human cancer cell lines over a 5-log dose range was –6.8 for **6e** and –7.36 for **6d**. Remarkably, the latter imidazole derivative, which is an isomer of **6e**, proved to be more cytotoxic than CA-4 (**1**, MG_MID Log GI_{50} –7.00)[13] and all the other imidazole derivatives tested thus far.

Conclusions

In this study, we have developed a general procedure for the highly regioselective synthesis of 4,5-diaryl-1-methyl-1*H*-imidazoles in three steps starting from inexpensive commercially available materials. The most important characteristics of this new procedure, which compares favourably with those previously developed to prepare this interesting class of imidazole derivatives,[8j,15] include high yields of operationally simple reactions, very high regioselectivity, and the possibility to introduce electron-neutral, electron-rich, or electron-deficient (hetero)aryl moieties at the 4- and/or

Table 6. Suzuki-type reactions of bromoimidazoles **11** with arylboronic acids **12**.



Entry	Bromoimidazole **11**	Ar^1	Arylboronic acid **12**	Ar^2	Pd derivative	Reaction time [h]	Reaction temp. [°C]	Product **6**	Yield [%]
1	**11a**	4-$MeOC_6H_4$	**12a**	C_6H_5	$PdCl_2(PPh_3)_2$[a]	48	60	**6c**	91
2	**11c**	2-naphthyl	**12b**	3,4,5-$(MeO)_3C_6H_2$	$PdCl_2(PPh_3)_2$[a]	72	60	**6e**	54
3	**11b**	3,4,5-$(MeO)_3C_6H_2$	**12c**	2-naphthyl	$PdCl_2(PPh_3)_2$[a]	168	60	**6d**	55
4	**11d**	3-pyridyl	**12d**	4-FC_6H_4	$PdCl_2$(dppf)[b]	24	reflux	**6g**	99
5	**11c**	2-naphthyl	**12b**	3,4,5-$(MeO)_3C_6H_2$	$PdCl_2$(dppf)[b]	24	reflux	**6e**	90
6	**11b**	3,4,5-$(MeO)_3C_6H_2$	**12c**	2-naphthyl	$PdCl_2$(dppf)[b]	24	reflux	**6d**	99
7	**11f**	4-ClC_6H_4	**12e**	2,4-$Cl_2C_6H_3$	$PdCl_2$(dppf)[b]	24	reflux	**6h**	42
8	**11b**	3,4,5-$(MeO)_3C_6H_2$	**12f**	3-F,4-$MeOC_6H_3$	$PdCl_2$(dppf)[b]	24	reflux	**6i**	84
9	**11b**	3,4,5-$(MeO)_3C_6H_2$	**12g**	6-MeO-2-naphthyl	$PdCl_2$(dppf)[b]	19	reflux	**6j**	83
10	**11e**	6-MeO-2-naphthyl	**12h**	4-$MeCOC_6H_4$	$PdCl_2$(dppf)[b]	24	reflux	**6k**	86
11	**11g**	C_6H_5	**12a**	C_6H_5	$PdCl_2$(dppf)[b]	24	reflux	**6f**	68

[a] $PdCl_2(PPh_3)_2$ was employed as the catalyst precursor in Method A. The reactions according to this method (Entries 1–3) were performed in a mixture of toluene and water at 60 °C. [b] $PdCl_2$(dppf) was employed as the catalyst precursor in Method B. The reactions according to this method (Entries 4–11) were performed in a refluxing mixture of toluene and water.

5-position of the imidazole ring. Remarkably, two 4,5-diaryl-1-methyl-1*H*-imidazoles prepared in this study have proven to be highly cytotoxic against human tumor cell lines, and one of these compounds was significantly more cytotoxic than naturally-occurring combretastatin-A4 and all of the imidazole derivatives tested thus far. Finally, it is worth mentioning that in the context of this investigation, we succeeded in the development of a general and efficient method for the concise synthesis of diversified 5-aryl-1-methyl-1*H*-imidazoles from commercially available 1-methyl-1*H*-imidazole and activated, unactivated, and deactivated aryl bromides. This new protocol has proven to be significantly more regioselective than the Pd-catalyzed arylation reactions of 1-methyl-1*H*-imidazole previously described in the literature.[20]

Experimental Section

General Procedure for the Pd-Catalyzed Synthesis of 5-Aryl-1-methyl-1*H*-imidazoles 10a, 10b, and 10c from 1-Methyl-1*H*-imidazole (7) and Aryl Halides 8a, 8b, and 9a, Respectively, in Toluene with CsF as the Base: The appropriate aryl halide **8** (2.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), P(2-furyl)$_3$ (23.2 mg, 0.1 mmol), and CsF (303.8 mg, 2.0 mmol) were placed in a reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated twice. Deaerated 1-methyl-1*H*-imidazole (**7**, 82.1 mg, 1.0 mmol) and dry toluene (5 mL) were then added successively by syringe under a stream of argon, and the resulting reaction mixture was stirred for 48 h under argon at 110 °C. The reaction was monitored by GLC and GLC/MSD analyses of a filtered sample of the reaction mixture. After being cooled to room temperature, the mixture was filtered through Celite and concentrated under reduced pressure, and the residue was purified by MPLC on silica gel. This procedure was used to prepare 5-(4-methoxyphenyl)-1-methyl-1*H*-imidazole (**10a**) from **7** and 4-iodoanisole (**8a**), 1-methyl-5-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (**10b**) from **7** and 5-iodo-1,2,3-trimethoxybenzene (**8b**), and 1-methyl-5-(2-naphthyl)-1*H*-imidazole (**10c**) from **7** and 2-bromonaphthalene (**9a**, Scheme 1).

5-(4-Methoxyphenyl)-1-methyl-1*H*-imidazole (10a): The crude reaction product obtained in Scheme 1 from the Pd-catalyzed reaction of **7** with **8a** was purified by MPLC on silica gel with CH_2Cl_2/methanol (95:5) as the eluent to give **10a** (99.7 mg, 66%) as a pale yellow solid: m.p. 106–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (s, 1 H), 7.31 (m, 2 H), 7.04 (s, 1 H), 6.97 (m, 2 H), 3.84 (s, 3 H), 3.63 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 159.4, 138.6, 133.2, 128.7 (2 C), 127.5, 122.2, 114.1 (2 C), 55.3, 32.3 ppm. EI-MS: *m*/*z* (%) = 189 (13), 188 (100), 174 (9), 173 (77), 145 (13). $C_{11}H_{12}N_2O$ (188.23): calcd. C 70.19, H 6.43, N 14.88; found C 70.09, H 6.37, N 14.73.

1-Methyl-5-(2-naphthyl)-1*H*-imidazole (10c): The crude reaction product obtained from the Pd-catalyzed reaction of **7** with **9a** (see Scheme 1) was purified by MPLC on silica gel with CH_2Cl_2/methanol (95:5) as the eluent to give **10c** (149.7 mg, 72%) as a pale yellow solid: m.p. 109–111 °C (ref.[25] 103 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (m, 4 H), 7.51 (m, 4 H), 7.21 (s, 1 H), 3.70 (s, 1 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 139.4, 133.4, 132.8, 128.7, 128.6 (2 C), 128.1, 127.9 (2 C), 127.3, 126.8, 126.5, 126.4, 32.8 ppm. EI-MS: *m*/*z* (%) = 209 (16), 208 (100), 207 (12), 180 (15), 166 (12). The ^{1}H NMR spectroscopic data of this compound were in agreement with those previously reported.[25]

General Procedure for the Pd-Catalyzed Synthesis of 5-Aryl-1-methyl-1*H*-imidazoles 10 from 7 and Aryl Bromides 9 in DMF with K_2CO_3 as the Base: The appropriate aryl bromide **9** (1.5 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), P(2-furyl)$_3$ (23.2 mg, 0.1 mmol), and K_2CO_3 (27.6 mg, 2.0 mmol) were placed in a reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated twice. Deaerated 1-methyl-1*H*-imidazole (**7**, 82.1 mg, 1.0 mmol) and deaerated DMF (5 mL) were then added successively by syringe under a stream of argon, and the resulting mixture was stirred at 110 °C for the period of time reported in Table 4. After this period, the reaction, monitored by GLC and

GLC/MS analyses of a filtered sample of the reaction mixture, was complete. The reaction mixture was then cooled to room temperature, diluted with AcOEt/CH_2Cl_2 (1:1, 80 mL), and filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by MPLC on silica gel. This procedure was used to prepare **10a**–**g** (Table 4).

1-Methyl-5-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (10b): The crude reaction product obtained in Entry 2 of Table 4 from the Pd-catalyzed reaction of **7** with 5-bromo-1,2,3-trimethoxybenzene (**9c**) was purified by MPLC on silica gel with CH_2Cl_2/methanol (95:5) as the eluent to give **10b** (136.4 mg, 55%) as a yellow solid: m.p. 115–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, 1 H), 7.07 (s, 1 H), 6.59 (s, 2 H), 3.89 (s, 1 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 153.2 (2 C), 138.9, 138.0, 133.4, 128.7, 125.3, 106.1 (2 C), 60.8, 56.2 (2 C), 32.4 ppm. EI-MS: *m*/*z* (%) = 249 (15), 248 (100), 234 (10), 205 (19), 190 (14). $C_{13}H_{16}N_2O_3$ (248.28): calcd. C 62.89, H 6.49, N 11.28; found C 62.73, H 6.35, N 11.14.

This same compound was prepared in 56% yield by the Pd-catalyzed reaction of **7** with 5-iodo-1,2,3-trimethoxybenzene (**8b**) in toluene at 110 °C with CsF as the base (Scheme 1).

1-Methyl-5-[4-(trifluoromethyl)phenyl]-1*H*-imidazole (10e): The crude reaction product obtained in Entry 5 of Table 4 from the Pd-catalyzed reaction of **7** with 1-bromo-4-(trifluoromethyl)benzene (**9e**) was purified by MPLC on silica gel with CH_2Cl_2/methanol (94:6) as the eluent to give **10e** (167.4 mg, 74%) as a pale yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.69 (m, 2 H), 7.52 (m, 3 H), 7.17 (s, 1 H), 3.71 (s, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 140.0, 133.5, 132.2, 129.2 (2 C), 129.0, 128.4 (2 C), 125.8 (q, *J* = 382 Hz, CF_3), 121.4, 32.7 ppm. EI-MS: *m*/*z* (%) = 227 (13), 226 (100), 198 (13), 186 (9), 171 (10). $C_{11}H_9F_3N_2$ (226.20): calcd. C 58.41, H 4.01, N 12.38; found C 58.37, H 3.85, N 12.34.

5-(6-Methoxynaphthalen-2-yl)-1-methyl-1*H*-imidazole (10g): The crude reaction product obtained in Entry 7 of Table 4 from the Pd-catalyzed reaction of **7** with 6-methoxy-2-bromonaphthalene (**9g**) was purified by MPLC on silica gel with CH_2Cl_2/methanol (95:5) as the eluent to give **10g** (166.8 mg, 70%) as a pale yellow solid: m.p. 157–159 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.76 (m, 3 H), 7.53 (s, 1 H), 7.44 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.18 (m, 3 H), 3.92 (s, 3 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 178.8, 158.0, 138.9, 133.7, 129.7, 129.1, 128.7, 128.4, 127.3, 126.7, 124.9, 119.4, 105.6, 55.3, 32.5 ppm. EI-MS: *m*/*z* (%) = 239 (17), 238 (100), 223 (35), 195 (28), 127 (7). $C_{15}H_{14}N_2O$ (238.28): calcd. C 75.61, H 5.92, N 11.76; found C 75.54, H 5.87, N 11.68.

2,5-Bis(4-methoxyphenyl)-1-methyl-1*H*-imidazole (15a): 4-Bromoanisole (**9b**) (374.0 mg, 2.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), P(2-furyl)$_3$ (23.2 mg, 0.1 mmol), and K_2CO_3 (276.2 mg, 2.0 mmol) were placed in a reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and backfilled with argon, and this sequence was repeated twice. Deaerated DMF (5 mL), pivalic acid (307.0 mg, 0.3 mmol) and 1-methyl-1*H*-imidazole (**7**, 82.1 mg, 1.0 mmol) were then sequentially added by syringe under a stream of argon, and the resulting mixture was stirred at 110 °C for 24 h. It was then cooled to room temperature, diluted with CH_2Cl_2/AcOEt (1:1, 50 mL), and filtered through Celite. The filtrate was concentrated under reduced pressure, and the solid residue was purified by MPLC on silica gel with CH_2Cl_2/methanol (95:5) as the eluent to give **15a** (64.7 mg, 22%) as a pale yellow solid: m.p. 138–139 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.62 (m, 2 H), 7.37 (m, 2 H), 7.11 (s, 1 H), 7.02 (m, 2 H), 6.97 8 (m, 2 H), 3.86 (s, 6 H), 3.62 (s, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 159.9, 159.4, 148.8, 130.4, 130.1 (4 C), 126.7, 123.6, 122.8, 114.2 (2 C), 114.0 (2 C), 55.4 (2 C), 33.6 ppm. EI-MS: *m*/*z* (%) = 295 (20), 294 (100), 293 (34), 279 (38), 147 (11). $C_{18}H_{20}N_2O_2$ (294.35): calcd. C 73.45, H 6.16, N 9.52; found: C 73.33, H 6.04, N 9.38.

1,4-Bis(1-methyl-1*H*-imidazol-5-yl)benzene (17): The crude reaction product obtained from the reaction of **7** (164.2 mg, 2.0 mmol) with 1,4-dibromobenzene (**9k**) (236.0 mg, 1.0 mmol) in DMF at 110 °C for 65 h, with 5 mol-% $Pd(OAc)_2$, 10 mol-% P(2-furyl)$_3$, and 2.0 equiv. of K_2CO_3, was purified by recrystallization from acetonitrile to give **17** (192.8 mg, 81%) as a yellow solid: m.p. 233–235 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.74 (s, 2 H), 7.58 (s, 4 H), 7.13 (s, 2 H), 3.72 (s, 6 H) ppm. ^{13}C NMR (50.3 MHz, [D$_6$]DMSO): δ = 140.8 (2 C), 132.9 (2 C), 129.6 (2 C), 128.7 (2 C), 127.7 (2 C), 33.2 (2 C) ppm. EI-MS: *m*/*z* (%) = 239 (21), 238 (100), 210 (8), 184 (8), 183 (8). $C_{14}H_{14}N_4$ (238.29): calcd. C 70.56, H 5.92, N 23.51; found C 70.51, H 5.80, N 23.39.

General Procedure for the Synthesis of 5-Aryl-4-bromo-1-methyl-1*H*-imidazoles 11: *N*-Bromosuccinimide (186.9 mg, 1.05 mmol) was added to a solution of a 5-aryl-1-methyl-1*H*-imidazole **10** (1.0 mmol) in dry acetonitrile (2 mL) at room temperature, and the resulting mixture was stirred at 20 °C for the period of time reported in Table 5. After this period, the reaction, monitored by GLC and GLC/MS analyses of a sample of the reaction mixture diluted with AcOEt, was complete. The reaction mixture was concentrated under reduced pressure, and the residue was purified by MPLC on silica gel. Compounds **11a**–**g** were prepared according to this general procedure (Table 5).

4-Bromo-1-methyl-5-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (11b): The crude reaction product obtained in Entry 3 of Table 5 from the C-4 bromination of **10b** with NBS was purified by MPLC on silica gel with CH_2Cl_2/methanol (99:1) as the eluent to give **11b** (235.5 mg, 72%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1 H), 6.59 (s, 2 H), 3.92 (s, 3 H), 3.89 (s, 6 H), 3.61 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 153.4 (2 C), 138.5, 137.2, 130.3, 123.3, 114.5, 107.4 (2 C), 60.9, 56.3 (2 C), 33.4 ppm. EI-MS: *m*/*z* (%) = 329 (14), 328 (96), 327 (15), 326 (100), 313 (58), 311 (59). $C_{13}H_{15}BrN_2O_3$ (327.17): calcd. C 37.72, H 4.62, Br 24.42; found C 47.58, H 4.55, Br 24.32.

4-Bromo-1-methyl-5-(2-naphthyl)-1*H*-imidazole (11c): The crude reaction product obtained in Entry 4 of Table 5 from the C-4 bromination of **10c** with NBS was purified by MPLC on silica gel with CH_2Cl_2/methanol (99:1) as the eluent to give **11c** (166.5 mg, 58%) as a yellow-orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (m, 4 H), 7.52 (m, 4 H), 3.61 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 137.4, 133.1, 133.0, 130.4, 129.6, 128.4, 128.1, 127.8, 127.1, 126.9, 126.7, 125.5, 115.0, 33.3 ppm. EI-MS: *m*/*z* (%) = 289 (15), 288 (96), 287 (18), 286 (100), 153 (19). $C_{14}H_{11}BrN_2$ (287.15): calcd. C 58.56, H 3.86, Br 27.83; found C 68.43, H 3.81, Br 27.71.

3-(4-Bromo-1-methyl-1*H*-imidazol-5-yl)pyridine (11d): The crude reaction product obtained in Entry 5 of Table 5 from the C-4 bromination of **10d** with NBS was purified by MPLC on silica gel with CH_2Cl_2/methanol (93:7) as the eluent to give **11d** (169.0 mg, 71%) as a yellow solid: m.p. 77–80 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.68 (s, 1 H), 7.78 (d, *J* = 7.8 Hz, 2 H), 7.49 (m, 2 H), 3.63 (s, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 150.4, 149.8, 138.3, 137.4, 137.4, 127.1, 125.9, 123.6, 116.2, 33.5 ppm. EI-MS: *m*/*z* (%) = 240 (11), 239 (97), 238 (12), 237 (100), 119 (16). $C_9H_8BrN_3$ (238.08): calcd. C 45.40, H 3.39, Br 33.56; found C 45.31, H 3.21, Br 33.43.

General Procedure for the Synthesis of 4,5-Diaryl-1-methyl-1*H*-imidazoles 6 from Bromoimidazoles 11 and Arylboronic Acids 12:

4,5-Diaryl-1-methyl-1*H*-imidazoles **6** were synthesized from bromoimoidazoles **11** and arylboronic acids **12** according two procedures: Method A and Method B.

Method A: A deaerated mixture of a bromoimidazole **11** (0.5 mmol), an arylboronic acid **12** (1.0 mmol), $PdCl_2(PPh_3)_2$ (17.6 mg, 0.025 mmol), $BnEt_3NCl$ (5.7 mg, 0.025 mmol), and CsF (227.8 mg, 1.5 mmol) in toluene (3.5 mL) and water (3.5 mL) was stirred at 60 °C under an atmosphere of argon for the period of time indicated in Table 6. After this period, a GLC/MS analysis of a sample of the reaction mixture, which was extracted with AcOEt, showed that the reaction was complete. The reaction mixture was then cooled to room temperature and extracted with AcOEt (4 × 39 mL). 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 required product. This method was used to prepare **6b**–**e** (Entries 1, 2, and 3, respectively, Table 6).

Method B: A deaerated mixture of a bromoimidazole **11** (0.5 mmol), an arylboronic acid **12** (1.0 mmol), $PdCl_2$(dppf) (20.4 mg, 0.025 mmol), $BnEt_3NCl$ (5.7 mg, 0.025 mmol), and CsF (227.8 mg, 1.5 mmol) in toluene (3.5 mL) and water (3.5 mL) was refluxed whilst stirring in an atmosphere of argon for the period of time reported in Table 6. After this period, a GLC/MS analysis of a sample of the reaction mixture, which was extracted with AcOEt, showed that the reaction was complete. The reaction mixture was then worked up and purified by a procedure very similar to that employed in Method A. Method B was used to prepare **6d**–**k** (Table 6, Entries 4–11).

1-Methyl-5-(naphthalen-2-yl)-4-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (6e): The crude reaction product obtained in Entry 5 of Table 6 from the Suzuki-type reaction of **11c** with 3,4,5-trimethoxyphenylboronic acid (**12b**), according to Method B was purified by MPLC on silica gel with CH_2Cl_2/methanol (97:3) as the eluent to give **6e** (168.3 mg, 90%) as a pale brown liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.80 (br. s, 1 H), 8.00 (d, J = 8.5 Hz, 1 H), 7.93 (s, 1 H), 7.92 (m, 1 H), 7.88 (m, 1 H), 7.61 (m, 1 H), 7.58 (m, 1 H), 7.45 (d, J = 8.5 Hz, 1 H), 6.83 (s, 2 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.52 (s, 6 H) ppm. ^{13}C NMR (150.3 MHz, $CDCl_3$): δ = 153.2 (2 C), 137.8, 136.0, 133.9, 133.4, 133.3, 130.8, 129.4, 128.9, 128.2, 127.9, 127.7, 127.5, 127.2, 125.3, 125.0, 104.1 (2 C), 60.8, 56.0 (2 C), 33.6 ppm. EI-MS: *m*/*z* (%) = 375 (26), 374 (100), 360 (21), 359 (84), 245 (10). $C_{23}H_{22}N_2O_3$ (374.43): calcd. C 73.78, H 5.92, N 7.48; found C 73.66, H 5.85, N 7.41.

This same compound was synthesized in 54% yield with Method A (Table 6, Entry 2).

1-Methyl-4-(naphthalen-2-yl)-5-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (6d): The crude reaction product obtained in Entry 6 of Table 6 from the Suzuki-type reaction of **11b** with 2-naphthylboronic acid (**12c**), according to Method B, was purified by MPLC on silica gel with CH_2Cl_2/methanol (97:3) as the eluent to give **6d** (185.3 mg, 99%) as an pale orange liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.26 (br. s, 1 H), 8.28 (d, J = 1.5 Hz, 1 H), 7.80 (m, 1 H), 7.75 (m, 1 H), 7.71 (d, J = 8.6 Hz, 1 H), 7.53 (dd, J = 8.6, 1.5 Hz, 1 H), 7.45 (m, 1 H), 7.44 (m, 1 H), 6.60 (s, 2 H), 3.96 (s, 3 H), 3.82 (s, 3 H), 3.80 (s, 6 H) ppm. ^{13}C NMR (150.3 MHz, $CDCl_3$): δ = 154.1 (2 C), 139.7, 136.0, 133.2, 133.0, 132.0, 129.6, 128.7, 128.4, 127.5, 126.81, 126.76, 126.5, 125.6, 124.1, 122.1, 107.9 (2 C), 61.1, 56.5 (2 C), 34.0 ppm. EI-MS: *m*/*z* (%) = 375 (26), 374 (100), 360 (5), 359 (19), 171 (6). $C_{23}H_{22}N_2O_3$ (374.43): calcd. C 73.78, H 5.92, N 7.48; found C 73.70, H 5.79, N 7.37.

This same compound was synthesized in 55% yield with Method A (Table 6, Entry 3).

3-[4-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl]pyridine (6g): The crude reaction product obtained in Entry 4 of Table 6 from the Suzuki-type reaction of **11d** with 4-fluorophenylboronic acid (**12d**) according to Method B was purified by MPLC on silica gel with CH_2Cl_2/methanol (93:7) as the eluent to give **6g** (125.2 mg, 99%) as a pale brown liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.65 (m, 2 H), 7.65 (m, 2 H), 7.38 (m, 3 H), 6.92 (m, 2 H), 3.54 (s, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 163.5, 150.5, 150.2, 149.4, 134.2, 133.0, 130.6 (2 C), 129.6, 128.3, 125.6, 122.9, 116.1 (2 C), 30.1 ppm. EI-MS: *m*/*z* (%) = 254 (17), 253 (100), 252 (60), 225 (10), 184 (28). $C_{15}H_{12}FN_3$ (253.27): calcd. C 71.13, H 4.78, N 16.59; found C 71.01, H 4.65, N 16.44.

4,5-Diphenyl-1-methyl-1*H*-imidazole (6f): The crude reaction product obtained in Entry 11 of Table 6 from the Suzuki-type reaction of **11g** with phenylboronic acid (**12a**), according to Method B, was purified by MPLC on silica gel with CH_2Cl_2/methanol (98:2) as the eluent to give **6f** (79.6 mg, 68%) as a pale yellow solid: m.p. 162–164 °C (ref.[26] 159–160 °C) ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.56 (s, 1 H), 7.51–7.13 (m, 10 H), 3.48 (s, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 138.3, 137.4, 134.7, 130.7 (2 C), 129.0 (2 C), 128.6, 128.4, 128.1 (2 C), 127.0, 126.6 (2 C), 126.3, 32.1 ppm. EI-MS: *m*/*z* (%) = 235 (17), 234 (100), 233 (68), 218 (17), 165 (43).

This same compound was synthesized in 62% yield by the *N*-methylation of commercially available 4,5-diphenyl-1*H*-imidazole (**5a**) with a very large molar excess of dimethyl carbonate at 100 °C for 48 h with K_2CO_3 (8 equiv.) and a catalytic amount of 18-crown-6 according to a literature procedure.[24]

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and characterization for **10d**, **10f**, **10h**, **10i**, **11a**, **11e**–**g**, **6c**, and **6h**–**k**. This material is available free of charge via the Internet.

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