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Regioselective Synthesis of 1,5-Diaryl-1*H*-imidazoles by Palladium-Catalyzed Direct Arylation of 1-Aryl-1*H*-imidazoles

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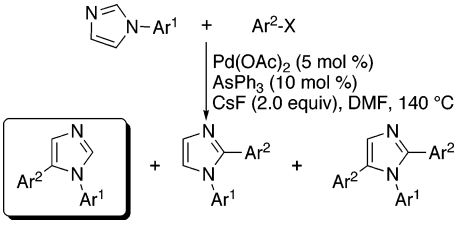

A variety of 1,5-diaryl-1*H*-imidazoles have been regioselectively synthesized by direct coupling of 1-aryl-1*H*-imidazoles with aryl iodides or bromides in DMF in the presence of CsF as the base and a catalyst precursor consisting of a mixture of $Pd(OAc)_2$ and $AsPh_3$. The data obtained in this synthetic study support a reaction mechanism involving an electrophilic attack of an arylpalladium(II) halide species onto the imidazole ring. Interestingly, some imidazole derivatives synthesized in this study have been found to exhibit significant cytotoxic activity against human tumor cell lines.

Introduction

In recent years, considerable attention has been directed to the palladium-catalyzed direct intermolecular C-arylation of π-excessive heteroaromatic compounds[1] such as furans,[2] thiophenes,[2b,c,3] oxazoles,[2a] thiazoles,[2a,4] imidazoles,[2a,4a,5] indoles,[5a,b,6] indolizines,[7] and imidazo[1,2-*a*]pyrimidine.[8] In fact, this method appears to have a synthetically significant advantage, being able to lead to carbon−carbon bond formation without involvement of stoichiometric amounts of organometallic reagents. However, the studies involving imidazoles have only been focused on the use of 1-methyl-1*H*-imidazole,[4a,5a] 1-benzyl-2-methyl-1*H*-imidazole,[5a] and 2-phenyl-1*H*-imidazole,[5c] and no reports on the palladium-catalyzed direct arylation of 1-aryl-1*H*-imidazoles **1** have been described to date.

It should also be noted that the results of the reaction of 1-methyl-1*H*-imidazole with bromo- or iodobenzene in

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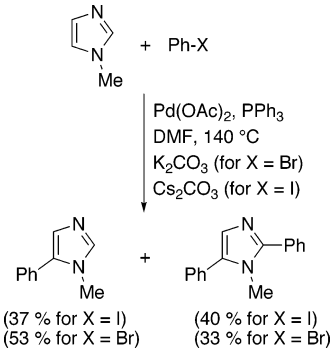
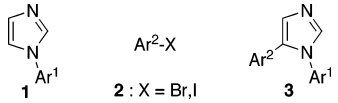
SCHEME 1

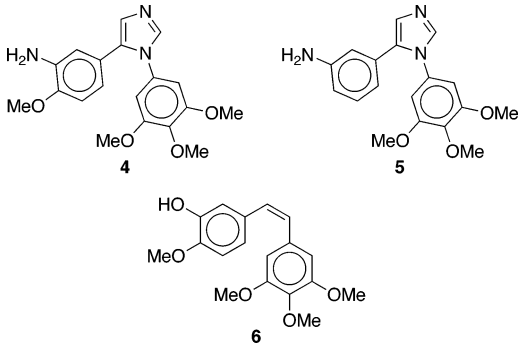


DMF at 140 °C, in the presence of 2 equiv of K_2CO_3 or Cs_2CO_3, respectively, and catalytic amounts of $Pd(OAc)_2$ and PPh_3,[5a] could lead us to believe that the palladium-catalyzed direct arylation of 1-substituted 1*H*-imidazoles has limited synthetic utility. In fact, this reaction furnishes 5-phenyl-1-methyl-1*H*-imidazole together with significant amounts of 2,5-diphenyl-1-methyl-1*H*-imidazole (Scheme 1).[5a]

Therefore, we set out to investigate the palladium-catalyzed direct arylation of 1-aryl-1*H*-imidazoles **1** with aryl halides **2**, and to develop an effective procedure for preparation of 1,5-diaryl-1*H*-imidazoles **3**, we examined the influence of factors such as the nature of the base to be used in the reaction, the ligand of the catalyst system, the type of halogen of the aryl halide **2**, the presence in **1** and/or **2** of an electron-donor or an electron-withdrawing group, the solvent, and the reaction temperature, which might influence the selectivity and efficiency of the reaction.



Our interest for the synthesis of compounds **3** was due to the fact that the methods reported so far in the literature for their preparation involve the construction of their imidazole ring by multistep sequences,[9] and yet no simple and straightforward synthesis has been reported. Moreover, 1,5-diaryl-1*H*-imidazoles include potent and selective cyclooxygenase-2 inhibitors[9e,10] and substances with antitubulin activity[9d] such as **4** and **5**, which represent cytotoxic *Z*-restricted analogues of combretastatin-A-4 (**6**).[11] This last compound is a constituent of the South African tree *Combretum caffrum* Kuntze (Combretaceae)[12] that inhibits both tubulin polymerization and the binding of colchicine to tubulin[13] and is also able to elicit selective and potent toxicity toward tumors' vasculature,[14] leaving normal vasculature intact.[14]



Finally, our aim was also to exclude the involvement of a Heck-type process in the palladium-catalyzed arylation of compounds **1** by confirming that the mechanism of this reaction is analogous to that proposed by Miura for arylation of azole compounds[5a] and involves an electrophilic attack to the most electron-rich position of compounds **1** by the arylpalladium halide species formed by oxidative addition of the aryl halide **2** to a palladium(0) species. In fact, conflicting mechanistic interpretations of the palladium-catalyzed direct C-arylation of π-excessive heteroarenes have been reported in the literature. A Heck-type mechanism has been suggested for arylation either of 3-carbalkoxyfurans and 3-carbalkoxythiophenes in toluene in the presence of KOAc and a catalytic amount of $Pd(PPh_3)_4$[2c] or of thiophenes, which contain a substituent such as CN, CHO, or NO_2, in an acetonitrile/water mixture in the presence of K_2CO_3, *n*-Bu_4NBr, and a catalytic amount of $Pd(OAc)_2$.[3a,b] However, there is also strong evidence that the palladium-catalyzed arylation of π-excessive heteroarenes such as 2-furaldehyde,[2d] imidazo[1,2-*a*]pyrimidine,[8] thiazole, and 1-methyl-1*H*-imidazole[4a] occurs at the site most susceptible to electrophilic attack. Therefore, in these and other similar cases[3b,5b] a mechanism involving an electrophilic aromatic substitution has to be considered as the most probable.

Results and Discussion

Our study of the synthesis of 1,5-diaryl-1*H*-imidazoles **3** via palladium-catalyzed reaction of compounds **1** with aryl halides was initiated by examining the reaction of commercially available 1-phenyl-1*H*-imidazole (**1a**) with 4-methoxy(pseudo)halobenzenes **2a**−**c** (Table 1), and at first, we performed this reaction under experimental

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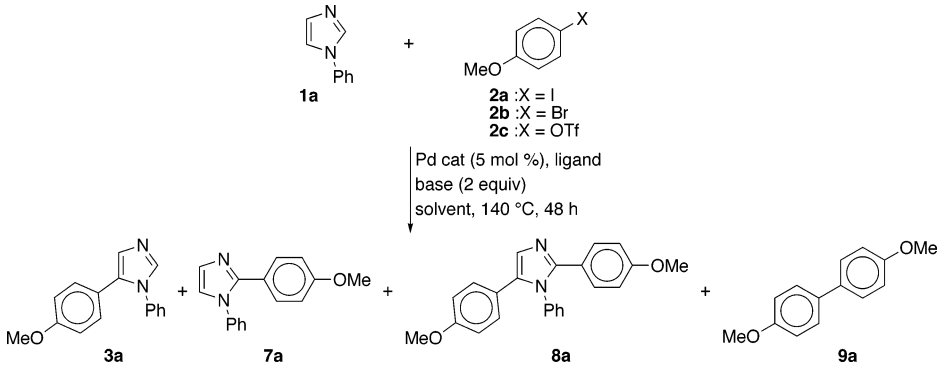
TABLE 1. Screening Reaction Conditions for the Selective C-5 Arylation of 1a with (Pseudo)halides 2a−c



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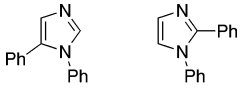
entry[a]	ligand	aryl (pseudo)halide	base	conversion of **1a**[b]	**3a/7a/8a/9a** GLC molar ratio	yield of **3a**[b] (%)	C-5 selectivity[c]
1	PPh_3	**2a**	Cs_2CO_3	63	61:11:8:20	39	0.76
2[d]	PPh_3	**2a**	Cs_2CO_3	60	70:15:0:15	35	0.82
3	PPh_3	**2b**	Cs_2CO_3	52	53:18:7:22	19	0.68
4	P(*o*-Tolyl)$_3$	**2a**	Cs_2CO_3	76	50:10:14:26	50	0.68
5	P(*t*-Bu)$_3$	**2a**	Cs_2CO_3	99	36:48:8:8	31	0.39
6[e]		**2a**	Cs_2CO_3	43	55:17:3:25	22	0.73
7[f]		**2a**	Cs_2CO_3	26	46:37:0:17	12	0.55
8[g]		**2a**	Cs_2CO_3	99	54:8:22:16	50	0.64
9	P(2-Furyl)$_3$	**2a**	Cs_2CO_3	89	75:8:4:13	39	0.86
10	$AsPh_3$	**2a**	Cs_2CO_3	75	63:13:3:21	37	0.80
11[h]	$AsPh_3$	**2a**	Cs_2CO_3	78	52:12:16:20	33	0.65
12	$AsPh_3$	**2a**	CsF	75	63:2:3:32	62	0.93
13[i]	$AsPh_3$	**2a**	CsF	65	84:9:0:7	49	0.90
14[j]	$AsPh_3$	**2a**	CsF	84	82:6:4:8	61	0.89
15	PPh_3	**2a**	CsF	89	61:1:2:36	40	0.95
16	$AsPh_3$	**2b**	CsF	81	82:2:11:5	61	0.86
17	$AsPh_3$	**2a**	K_3PO_4	47	58:12:5:25	27	0.77
18	PPh_3	**2b**	CsF	63	62:1:36:1	32	0.63
19	P(4-$CF_3C_6H_4$)$_3$	**2a**	CsF	87	77:6:0:17	43	0.93
20	dppb	**2a**	CsF	73	71:4:6:19	48	0.88
21	dppf	**2a**	CsF	57	37:5:2:56	26	0.84
22	dppf	**2c**	CsF	50	82:8:4:6	34	0.87
23	dppb	**2c**	CsF	27	80:7:0:13	9	0.92
24	dppb	**2a**	Cs_2CO_3	64	61:16:0:23	35	0.79
25	dppf	**2a**	Cs_2CO_3	72	50:6:13:31	41	0.72

[a] Unless otherwise reported, the reactions were run with 1 mmol of **1a**, 2 mmol of compounds **2a**−**c**, 5 mol % of $Pd(OAc)_2$, and 10 mol % of monodentate ligand or 5 mol % of bidentate ligand in 5 mL of DMF at 140 °C for 48 h. [b] Determined by GLC analysis with use of an internal standard (naphthalene). [c] The selectivity was expressed as the [**3a**/(**3a** + **7a** + **8a**)] molar ratio. [d] This reaction was performed using a 1.3:1 molar ratio between **2a** and **1a**. [e] This reaction was performed using 5 mol % o $Pd(PPh_3)_4$. [f] In this reaction, 2.5 mol % of *trans*-di(*μ*-acetato)bis[(di-*o*-tolylphosphino)benzyl]dipalladium(II) was used. [g] This reaction was carried out using 10 mol % of $Pd(OAc)_2$. [h] This reaction was run using a 4:1 molar ratio of $AsPh_3$ and $Pd(OAc)_2$. [i] This reaction was run in 5 mL of dioxane at 120 °C for 48 h. [j] This reaction was run in 5 mL of toluene at 110 °C for 48 h.

conditions very similar to those used by Miura and co-workers[5a] for C-arylation of 1-methyl-1*H*-imidazole. Thus, **1a** was reacted with 2 equiv of iodide **2a** and 2 equiv of Cs_2CO_3 in DMF in the presence of 5 mol % $Pd(OAc)_2$ and 10 mol % PPh_3 at 140 °C for 48 h (Table 1, entry 1). After this period of time, the conversion was found to be 63% and the reaction mixture proved to contain the triarylated imidazole **8a**, the expected monoarylation derivatives **3a** and **7a**, PPh_3, a significant amount of biphenyl **9a**, and very small amounts of imidazoles **3b** and **7b** and (4-methoxyphenyl)diphenylphosphine (**10**). It should be noted that compounds **8a** and **9a** were formed concomitantly with **3a** and **7a**.



$PPh_2(4\text{-}MeOC_6H_4)$

10

Compound **9a** presumably derived from a palladium-catalyzed Ullmann-type reductive coupling of **2a**[15,16] and

(15) It should be noted that Miura and co-workers[5a] did not mention the formation of a 2,5-diarylated compound in the palladium-catalyzed reaction of 1-methyl-1*H*-imidazole with iodo- or bromobenzene. Moreover, these Authors did not report the presence in the reaction mixtures of the homocoupling product derived from these halobenzenes.

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compounds **3b** and **7b** very likely derived from the reaction of **1a** with palladium complex **12** which was formed by an aryl−aryl exchange (eq 1)[17] between the palladium center and the PPh_3 ligand of palladium complex **11** obtained by oxidative addition of **2a** to catalytically active $Pd(PPh_3)_2(OAc)^-$.[18]

$$\underset{\mathbf{11}}{Pd(PPh_3)_2(4\text{-}MeOC_6H_4)I} \rightleftharpoons \underset{\mathbf{12}}{Pd(PPh_3)[PPh_2(4\text{-}MeOC_6H_4)]PhI} \quad (1)$$

On the other hand, phosphine **10** also likely derived from a palladium-catalyzed Pd-aryl/P-aryl exchange similar to that involved in the preparation of functionalized arylphosphines by phosphination of aryl bromides using triarylphosphines.[19]

Compound **3a** was obtained in 39% GLC yield and with a selectivity of 0.76 (Table 1, entry 1). Interestingly, pure compounds **3a**, **7a**, and **8a** could be isolated by chromatography on silica gel of this complex reaction mixture, and their structure could be unambiguously assigned on the basis of their ^1H and ^{13}C NMR spectra at 600 and 150 MHz, respectively, and by a combination of 2D NMR techniques that included $^1H-^{13}C$ heteronuclear single quantum coherence (HSQC) and $^1H-^{13}C$ heteronuclear multiple bond correlation (HMBC).

We then attempted to improve the conversion and selectivity of this palladium-catalyzed reaction to minimize the formation of byproducts and to successfully develop a general catalytic protocol for preparation of 1,5-diaryl-1*H*-imidazoles **3**. Thus, the effects of a number of variables such as the **2a/1a** molar ratio, the nature of the (pseudo)halogen substituent of compounds **2**, the base, the solvent, and the palladium derivative and its ligand were carefully examined. As far as the conversion is concerned, we found that running the reaction in the presence of 10 mol % of $Pd(OAc)_2$ under ligandless conditions (Table 1, entry 8) gave quantitative results after 48 h at 140 °C, but a large amount of **8a** was formed and **3a** was obtained in low selectivity. An almost quantitative conversion was also obtained using a mixture of $Pd(OAc)_2$ and P(*t*-Bu)$_3$ as the catalyst (Table 1, entry 5), but the yield of **3a** and the C-5 selectivity of the reaction proved to be very low. On the contrary, low conversion (< 30%) was obtained in the reaction carried out using Cs_2CO_3 as the base and a catalyst precursor consisting of the Herrmann's palladacycle[20] (Table 1, entry 7). In all of the other reactions performed using Cs_2CO_3 as the base, ca. 50−90% conversions were obtained after 48 h at 140 °C. We also found that when the reaction was run using a 1.3:1 molar ratio between **2a** and **1a** (Table 1, entry 2) its conversion was similar to that of entry 1, but compound **3a** was obtained in higher selectivity and **8a** was not formed. However, the yield of **3a** was lower; thus, we thought it right to perform all of the subsequent reactions using a 2:1 molar ratio between compounds **2** and **1a**. We also observed that the yield and selectivity of the reaction carried out under the experimental conditions of entry 1 were lowered either upon changing the electrophile form iodide **2a** to bromide **2b** (Table 1, entry 3) or using catalyst precursors such as $Pd(PPh_3)_4$ (Table 1, entries 6). On the other hand, when the PPh_3 ligand of the palladium catalyst precursor was replaced by P(*o*-Tolyl)$_3$ (Table 1, entry 4), P(*t*-Bu)$_3$ (Table 1, entry 5), P(2-furyl)$_3$ (Table 1, entry 9), P(4-$CF_3C_6H_4$)$_3$ (Table 1, entry 19), or $AsPh_3$ (Table 1, entries 10−14, 16, and 17), cleaner reaction mixtures were obtained that did not contain compounds derived from scrambling of the aryl moiety of **2a** with the organic group of the ligands.

We were then pleased to find that switching to CsF as the base and using DMF as solvent and a catalyst precursor consisting of a mixture of $Pd(OAc)_2$ and $AsPh_3$ in a 1:2 molar ratio (Table 1, entry 12) produced a significant increase of the selectivity of the reaction which in this case occurred in the homogeneous phase and allowed us to obtain **3a** in 62% yield. It should also be noted that results comparable with those of this entry could be obtained using dioxane or toluene as solvent (Table 1, entries 13 and 14, respectively), even though under these conditions the reaction occurred in the heterogeneous phase. Moreover, high selectivity was also observed when **2a** was reacted with **1a** in DMF in the presence of CsF and the catalyst precursor consisting of a mixture of $Pd(OAc)_2$ and PPh_3 (Table 1, entry 15) or a mixture of $Pd(OAc)_2$ and P(4-$CF_3C_6H_4$)$_3$ (Table 1, entry 19). However, in both these cases the yield was lower than that obtained in entry 12 of Table 1 and the reaction mixture obtained in entry 15 proved to be contaminated by compounds derived from scrambling of the aryl moiety of **2a** with the phenyl group of PPh_3.

Interestingly, satisfactory results could also be obtained by reaction of **1a** with bromide **2b** using the experimental conditions of entry 12 (Table 1, entry 16), but low selectivity and/or yields were obtained by treatment of **1a** with **2a** in the presence of the catalyst precursors consisting of a mixture of $Pd(OAc)_2$ and a bidentate phosphine ligand such as dppb (Table 1, entries 20, 23, and 24) or dppf (Table 1, entries 21 and 25). On the other hand, unsatisfactory results were obtained in the reactions of **1a** with triflate **2c** in DMF in the presence of CsF and catalytic amounts of $Pd(OAc)_2$ and dppf (Table 1, entry 22) or dppb (Table 1, entry 23).

Having successfully demonstrated the viability of the $Pd(OAc)_2/AsPh_3$-catalyzed selective C-5 arylation of **1a** with iodide **2a** or bromide **2b** in the presence of CsF as the base, we then proceeded to test the scope and limitations of this arylation reaction by applying the optimized reaction conditions of entry 12 of Table 1 to the synthesis of 1,5-diaryl-1*H*-imidazoles **3** starting from 1-aryl-1*H*-imidazoles **1a**−**g** and commercially available iodides **2a** and **2d**−**j** or aryl bromides **2b** and **2k**−**m**.

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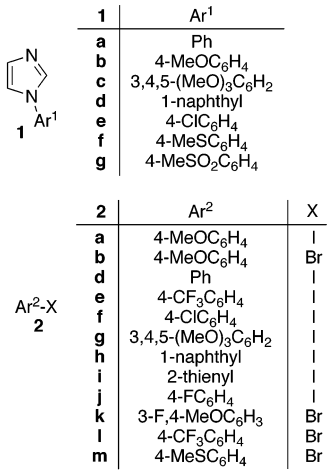


1	Ar^1
a	Ph
b	4-$MeOC_6H_4$
c	3,4,5-$(MeO)_3C_6H_2$
d	1-naphthyl
e	4-ClC_6H_4
f	4-$MeSC_6H_4$
g	4-$MeSO_2C_6H_4$

2	Ar^2	X
a	4-$MeOC_6H_4$	I
b	4-$MeOC_6H_4$	Br
d	Ph	I
e	4-$CF_3C_6H_4$	I
f	4-ClC_6H_4	I
g	3,4,5-$(MeO)_3C_6H_2$	I
h	1-naphthyl	I
i	2-thienyl	I
j	4-FC_6H_4	I
k	3-F,4-$MeOC_6H_3$	Br
l	4-$CF_3C_6H_4$	Br
m	4-$MeSC_6H_4$	Br

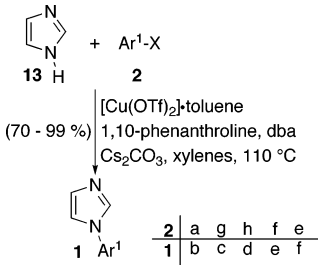
Although several methods have been reported in the literature for the synthesis of 1-aryl-1*H*-imidazoles **1**,[21] for preparation of compounds **1b**−**f** we preferred the method described in 1999 by Buchwald and co-workers[21b] owing to its effectiveness and simplicity. Thus, an aryl halide **2** was reacted with 1.5 equiv of imidazole (**13**) in xylenes at 110 °C in the presence of 1.1 equiv of Cs_2CO_3, 5 mol % of *trans,trans*-dibenzylideneacetone (dba), 1 equiv of 1,10-phenanthroline, and 5 mol % of $(CuOTf)_2$·toluene (Scheme 2).

Pure compounds **1b**,**d**,**e**,**f** were so obtained in 96−99% yield after chromatographic purification of the corresponding crude reaction mixtures. However, the chromatographic separation of **1c** from 1,10-phenanthroline proved to be difficult. Thus, in this case, the crude reaction mixture was first purified by chromatography on silica gel and a CH_2Cl_2 solution of the product obtained by concentration of the collected chromatographic fractions was subsequently treated with a 1 M aqueous $CuCl_2$ solution and then washed with water. Concentration of the resultant CH_2Cl_2 solution allowed us to obtain pure **1c** in 70% yield.

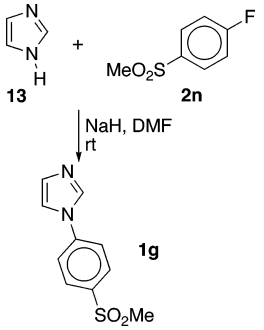
On the other hand, **1g** was synthesized in 62% yield by reaction of **13** with 1.03 equiv of NaH in DMF followed by treatment with 1.03 equiv of fluoride **2n** (Scheme 3).

Table 2 summarizes the results of the reactions performed to prepare 1,5-diaryl-1*H*-imidazoles **3a**−**n**. It should be noted that these reactions, unlike those reported in Table 1, were stopped when they did not further progress. As illustrated in this table, the established procedure provided a quick entry to compounds **3a**−**d**,**f**,**h**−**j**,**l**,**m** and allowed us to obtain all these 1,5-diaryl-1*H*-imidazoles, except **3m**, in moderate yields and high or complete selectivity. On the contrary, compound **3m** was obtained in very low yield and selectivity since, unexpectedly, its preparation from **1f** and **2j** (Table 2, entry 17) furnished the C-2 arylation product, **7m**, as the main component of the reaction mixture.

SCHEME 2



SCHEME 3



3c : Ar^1 = Ph; Ar^2 = 4-$CF_3C_6H_4$
3d : Ar^1 = Ph; Ar^2 = 4-ClC_6H_4
3f : Ar^1 = Ar^2 = 4-$MeOC_6H_4$
3h : Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 4-$MeOC_6H_4$
3i : Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 2-naphthyl
3j : Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 3-F,4-$MeOC_6H_3$
3l : Ar^1 = 4-ClC_6H_4; Ar^2 = 4-$MeOC_6H_4$
3m : Ar^1 = 4-$MeSC_6H_4$; Ar^2 = 4-FC_6H_4

7c : Ar^1 = Ph; Ar^2 = 4-$CF_3C_6H_4$
7d : Ar^1 = Ph; Ar^2 = 4-ClC_6H_4
7f : Ar^1 = Ar^2 = 4-$MeOC_6H_4$
7h : Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 4-$MeOC_6H_4$
7m : Ar^1 = 4-$MeSC_6H_4$; Ar^2 = 4-FC_6H_4

The structural assignment of 1,5-diaryl-1*H*-imidazoles **3a**−**d**,**f**,**h**−**j**,**l**,**m** was performed on the basis of their ^1H and ^{13}C NMR spectra at 600 and 150 MHz, respectively, and by a combination of 2D NMR techniques which included $^1H-^{13}C$ HSQC and $^1H-^{13}C$ HMBC.

Moreover, the ^{13}C NMR data of these imidazole derivatives indicate that C-5 generally resonates at a higher field than C-2 and that C-4 resonates at an intermediate field with respect to C-2 and C-5. On the other hand, the structures of 1,2-diaryl-1*H*-imidazoles **7a**−**d**,**f**,**h**,**m** and those of 1,2,5-triaryl-1*H*-imidazoles **8a**−**c**,**f**,**h**,**j**, which were obtained as coproducts of the palladium-catalyzed reactions reported in Table 2, were preliminarily established on the basis of their EI-MS spectra. However, the structural assignments of compounds **7f** and **8h** were

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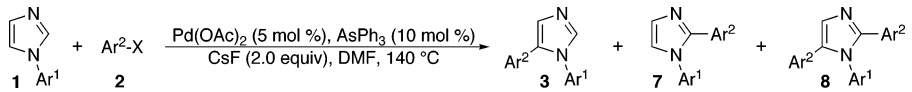
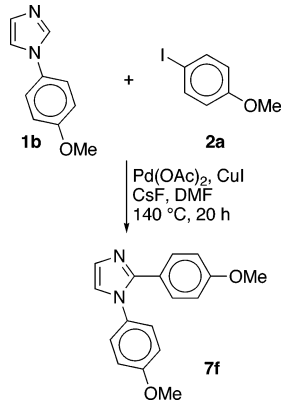
TABLE 2. Palladium-Catalyzed Synthesis of 1,5-Diaryl-1*H*-imidazoles 3 from 1-Aryl-1*H*-imidazoles 1 and Aryl Halides 2



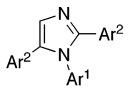
	reagents						products		
entry	**1**	Ar^1	**2**	Ar^2	X	reaction time (h)	**3/7/8** GLC molar ratio	**3**	isolated yield (%)
1	**1a**	Ph	**2a**	4-$MeOC_6H_4$	I	42	95:5:0	**3a**	49
2	**1a**	Ph	**2b**	4-$MeOC_6H_4$	Br	48	100:0:0	**3a**	43
3	**1a**	Ph	**2d**	Ph	I	23	86:3:11	**3b**	41
4	**1a**	Ph	**2e**	4-$CF_3C_6H_4$	I	17	86:5:9	**3c**	38
5	**1a**	Ph	**2l**	4-$CF_3C_6H_4$	Br	66	76:0:24	**3c**	59
6	**1a**	Ph	**2f**	4-ClC_6H_4	I	67	94:6:0	**3d**	39
7	**1a**	Ph	**2i**	2-thienyl	I	67	100: 0:0	**3e**	*a*
8	**1b**	4-$MeOC_6H_4$	**2a**	4-$MeOC_6H_4$	I	20	88:3:9	**3f**	36
9	**1b**	4-$MeOC_6H_4$	**2b**	4-$MeOC_6H_4$	Br	91	52:11:37	**3f**	22
10	**1b**	4-$MeOC_6H_4$	**2g**	3,4,5-$(MeO)_3C_6H_2$	I	45		**3g**	*b*
11	**1c**	3,4,5-$(MeO)_3C_6H_2$	**2a**	4-$MeOC_6H_4$	I	21	87:2:11	**3h**	40
12	**1c**	3,4,5-$(MeO)_3C_6H_2$	**2b**	4-$MeOC_6H_4$	Br	46	100:0:0	**3h**	61
13	**1c**	3,4,5-$(MeO)_3C_6H_2$	**2h**	1-naphthyl	I	68	100:0:0	**3i**	55
14	**1c**	3,4,5-$(MeO)_3C_6H_2$	**2k**	3-F,4-$MeOC_6H_3$	Br	27	95:0:5	**3j**	72
15	**1d**	1-naphthyl	**2g**	3,4,5-$(MeO)_3C_6H_2$	I	240		**3k**	*b*
16	**1e**	4-ClC_6H_4	**2a**	4-$MeOC_6H_4$	I	166	100: 0:0	**3l**	36
17	**1f**	4-$MeSC_6H_4$	**2j**	4-FC_6H_4	I	116	17:43:40	**3m**	9
18	**1g**	4-$MeSO_2C_6H_4$	**2a**	4-$MeOC_6H_4$	I	93		**3n**	*b*
19	**1g**	4-$MeSO_2C_6H_4$	**2b**	4-$MeOC_6H_4$	Br	118		**3n**	*b*

[a] The crude reaction mixture contained a very small amount of **3e**. Thus, no attempt was made to isolate this compound. [b] Compound **1** was quantitatively recovered after the period of time reported in the table for this reaction.

SCHEME 4



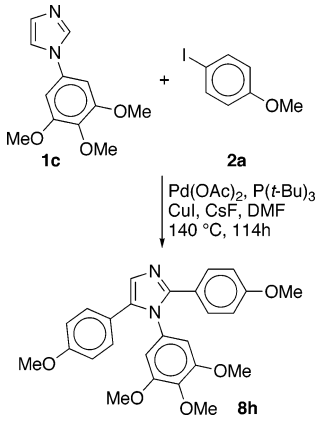
confirmed by independent syntheses using procedures very recently developed in our laboratory.[22]



8b : $Ar^1 = Ar^2 = Ph$
8c : $Ar^1 = Ph$; $Ar^2 = 4\text{-}CF_3C_6H_4$
8f : $Ar^1 = Ar^2 = 4\text{-}MeOC_6H_4$
8h : $Ar^1 = 3,4,5\text{-}(MeO)_3C_6H_2$; $Ar^2 = 4\text{-}MeOC_6H_4$
8j : $Ar^1 = 3,4,5\text{-}(MeO)_3C_6H_2$; $Ar^2 = 3\text{-}F,4\text{-}MeOC_6H_3$

In particular, reaction of **1b** with 2 equiv of **2a** in DMF at 140 °C for 20 h, in the presence of 10 mol % of $Pd(OAc)_2$, 2 equiv of CuI, and 2 equiv of CsF, furnished a reaction mixture which contained compounds **3f**, **7f**, and **8f** in a 3:78:19 molar ratio, respectively (Scheme 4).

SCHEME 5



Chromatographic purification allowed us to isolate **7f** in 34% yield. On the other hand, **8h** was prepared in 21% yield by treatment of **1c** with 3 equiv of **2a** in DMF at 140 °C for 114 h, in the presence of 10 mol % of $Pd(OAc)_2$, 20 mol % of P(*t*-Bu)$_3$, 3 equiv of CuI, and 3 equiv of CsF (Scheme 5).

The data of Table 2 also show that, in addition to several aryl iodides, aryl bromides **2b** and **2k** efficiently participated in the selective palladium-catalyzed C-5 arylation of 1-aryl-1*H*-imidazoles such as **1a** and **1c** (Table 2, entries 2 and 14). However, reaction of **2b** with **1b** furnished **3f** in unexpectedly low yield and selectivity (Table 2, entry 9). This reaction, similar to that reported in entry 17 of Table 2, furnished a large amount of the C-2 arylation product.

Remarkably, the palladium-catalyzed C-5 arylation of compounds **1** proved to be highly sensitive to electronic effects, and according to the mechanism proposed by Miura and co-workers for arylation of azole compounds,[5a] it was most efficient when compounds **1** having an electron-rich aryl group linked to N-1 were used as

(22) The synthesis of 1,2-diaryl-1*H*-imidazoles and 1,2,5-triaryl-1*H*-imidazoles by palladium- and copper-mediated reaction of 1-aryl-1*H*-imidazoles with aryl halides will be described in detail in a forthcoming paper.

substrates. On the other hand, no reaction occurred when imidazole **1** was characterized by a strong electron-withdrawing group such as 4-$MeSO_2C_6H_4$ (Table 2, entries 18 and 19). It should also be noted that activated, unactivated and moderately deactivated aryl halides such as **2e**, **2d**, and **2a**, respectively, were tolerated as electrophilic partners of the arylation reaction, but strongly deactivated iodide **2g** proved to be unable to participate to the reaction (Table 2, entries 10 and 15). This was also hampered by the presence of a sulfur-containing aryl group in **1** (Table 2, entries 17−19) or a sulfur-containing electrophile such as **2i** (Table 2, entry 7).

Finally, it is worth mentioning that some compounds synthesized in this study were tested in vitro for cytotoxicity against the NCI three-cell line panel consisting of MCF7, SF-268, and NCI-H460, and compounds which reduced the growth of any one of these cell lines to 32% or less were considered active and passed on for evaluation over a 5-log dose range in the NCI's in vitro human disease-oriented tumor cell line screening panel that consisted of 60 human tumor cell lines. 1,5-Diaryl-1*H*-imidazoles **3c**, **3f**, and **3h**, 1,2-diaryl-1*H*-imidazole **7f**, and 1-aryl-1*H*-imidazole **1c** were found to be significantly cytotoxic, but among the compounds tested, **3h**, which represents a *Z*-restricted analogue of combretastatin A-4 (**6**), proved to be the most potent (MG-MID log GI_{50} = −7.09).

Conclusion

In conclusion, this work has demonstrated that a variety of 1,5-diaryl-1*H*-imidazoles can be selectively synthesized in moderate yields by direct palladium-catalyzed C-arylation of 1-aryl-1*H*-imidazoles with aryl iodides or bromides. This preparation method, which is quite simple and practical, favorably competes with those previously described in the literature which are based on the construction of the imidazole ring,[9] even though it suffers from a limitation due to the fact that this Pd-catalyzed arylation is hampered by the presence of a sulfur atom in the imidazole substrate or the electrophile.

Data have also been obtained in support of the reaction mechanism proposed by Miura[5a] for arylation of azoles, which involves an electrophilic attack of an arylpalladium halide species onto position C-5 of the heteroaromatic ring. This position has been reported to be more reactive then C-4 and C-2 in electrophilic substitution reactions.[5a] The arylpalladium(II) species can be generated from an activated, unactivated, or moderately deactivated aryl bromide or iodide. Moreover, strongly deactivated 3,4,5-trimethoxyphenyl iodide has been proven to be unable to participate to the arylation reaction of 1-aryl-1*H*-imidazoles, and compound **1g**, which possesses a strong electron-withdrawing group at its N-1, did not undergo the Pd-catalyzed reaction.

It is also worth mentioning that some imidazole derivatives synthesized in this study have been found to be cytotoxic against human cancer cell lines and that one among these substances exhibited potent activity.

Further studies on the highly selective synthesis of potentially cytotoxic imidazole derivatives by direct C-arylation reactions are underway.

Experimental Section

General Procedure for the Synthesis of 1-Aryl-1*H*-imidazoles 1b−f. To a flame-dried reaction vessel were added imidazole (**13**) (2.04 g, 30.0 mmol), 1,10-phenanthroline (3.60 g, 20.0 mmol), *trans,trans*-dibenzylidene acetone (dba) (0.23 g, 1.0 mmol), Cs_2CO_3 (7.17 g, 22.0 mmol), copper(I) trifluomethanesulfonate toluene complex (0.52 g, 1.0 mmol), and an aryl iodide **2** (20.0 mmol), if a solid. The reaction vessel was fitted with a silicon septum, evacuated, and back-filled with argon, and this sequence was repeated twice. Xylenes (4 mL) and an aryl iodide **2** (20.0 mmol), 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 110 °C until GLC analysis showed that the reaction was complete (24−91 h). The resultant heterogeneous mixture was allowed to cool to room temperature, diluted with EtOAc, filtered through a plug of silica gel, and eluted with additional EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by MPLC on silica gel to provide the desired product. This procedure allowed us to prepare compounds **1b**,**d**−**f** in 96−99% yield. However, the chromatographic separation of **1c** from 1,10-phenanthroline proved to be difficult. Thus, the chromatographic fractions that corresponded to the purification of **1c** using a 96:4 mixture of CH_2Cl_2 and methanol as eluent were collected, concentrated, and then dissolved in CH_2Cl_2. The resultant solution was thoroughly washed with a 1 M aqueous $CuCl_2$ solution and water, dried, filtered over Celite, and concentrated under reduced pressure. Chemically pure **1c** was so obtained in 70% yield.

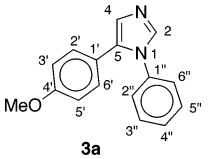
Characterization of compounds **1b**−**f** can be found in the Supporting Information.

1-[4-(Methylsulfonyl)phenyl]-1*H*-imidazole (1g). A 60% suspension of NaH in mineral oil (0.80 g, 20.0 mmol) was washed with pentane (5 mL), and the resultant solid was suspended in DMF (20 mL) and treated under argon with a solution of imidazole (**13**) (1.33 g, 19.5 mmol) in DMF (10 mL). The mixture was stirred for 20 min at room temperature, and then a solution of 1-fluoro-4-(methylsulfonyl)benzene (**2n**) (3.48 g, 19.2 mmol) in DMF (5 mL) was added during 4 min. The resultant mixture was stirred for 19 h at room temperature and then poured into an ice-cooled saturated NH_4Cl solution and extracted with EtOAc. The organic extract was washed with water, dried, and concentrated under reduced pressure, and the residue was purified by MPLC on silica gel with a 96:4 mixture of CH_2Cl_2 and methanol as eluent to give **1g** (2.56 g, 62%) as a colorless solid: mp 180−181 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.11 (s, 1H, H-2), 8.03 (m, 2H, H-3′ and H.5′), 7.63 (m, 2H, H-2′ and H-6′), 7.40 (br s, 1H, H-5), 7.27 (br s, 1H, H-4), 3.12 (s, 3H, Me); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 141.2, 139.0, 135.3, 131.4, 129.5 (2C), 121.3 (2C), 117.6, 44.5; IR (KBr) ν_{max} 1596, 1510, 1421, 1145, 953, 840, 779 cm^{-1}; EI-MS: *m/z* 223 (13), 222 (100), 207 (21), 159 (15), 143 (32), 132 (13), 116 (43), 89 (17), 63 (8). Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53. Found: C, 53.98; H, 4.58.

General Procedure for the Palladium-Catalyzed Synthesis of 1,5-Diaryl-1*H*-imidazoles 3 from Compounds 1 and Aryl Halides 2. To a flame-dried reaction vessel were added compound **1** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), CsF (0.30 g, 2.0 mmol), $AsPh_3$ (30.6 mg, 0.1 mmol), and an aryl iodide or bromide **2** (2.0 mmol), if a solid. The reaction vessel was fitted with a silicon septum, evacuated, and back-filled with argon, and this sequence was repeated twice. DMF (5 mL) and an aryl iodide or bromide **2** (2.0 mmol), if a liquid, were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was stirred at 140 °C under argon 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 crude reaction mixture treated with a saturated aqueous NaCl solution and extracted with AcOEt. After being cooled to room temperature, the reaction mixture was diluted with AcOEt, poured into a

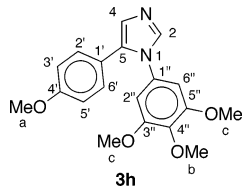
saturated aqueous NaCl solution, and extracted with AcOEt. The organic extract was washed with water, dried, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. 1,5-Diaryl-1*H*-imidazoles **3a**, **3h**, and **3i** are representative of those prepared using this procedure.

5-(4-Methoxyphenyl)-1-phenyl-1*H*-imidazole (3a). The crude reaction product, which was obtained in entry 1 of Table 2 by palladium-catalyzed reaction of **1a** with **2a**, was purified by MPLC on silica gel with a mixture of toluene and EtOAc (50:50 + 0.1% Et_3N) as eluent to give **3a** (0.12 g, 49%) as a white solid: mp 121−123 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (br s, 1H, H-2), 7.40 (m, 2H, H-3″ and H-5″), 7.38 (m, 1H, H-4″), 7.22 (br s, 1H, H-4), 7.19 (m, 2H, H-2″ and H-6″), 7.06 (m, 2H, H-2′ and H-6′), 6.79 (m, 2H, H-3′ and H-5′), 3.78 (s, 3H, OMe); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3 (C-4′), 138.0 (C-2), 136.5 (C-1″), 132.9 (C-5), 129.6 (C-3″ and C-5″), 129.5 (C-2′ and C-6′), 128.3 (C-4″), 127.1 (C-4), 125.6 (C-2″ and C-6″), 121.4 (C-1′), 114.0 (C-3′ and C-5′), 55.2 (OMe); IR (KBr) ν_{max} 2982, 1614, 1515, 1255, 1181, 1027, 807 cm^{-1}; EI-MS *m/z* 251 (17), 250 (100), 235 (44), 208 (15), 207 (26), 180 (10), 77 (14), 40 (12). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 77.78; H, 5.64. Found: C, 77.61; H, 5.57.



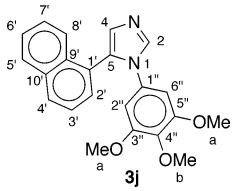
3a

5-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (3h). The crude reaction product, which was obtained in entry 12 of Table 2 by palladium-catalyzed reaction of **1c** with **2b**, was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (97:3) as eluent to give **3h** (0.21 g, 61%) as an orange low-melting solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (br s, 1H, H-2), 7.21 (br s, 1H, H-4), 7.09 (d, J = 8.7 Hz, 2H, H-2′ and H-6′), 6.82 (d, J = 8.7 Hz, 2H, H-3′ and H-5′), 6.38 (s, 2H, H-2″ and H-6″), 3.86 (s, 3H, OMe_c), 3.79 (s, 3H, OMe_a), 3.71 (s, 3H, OMe_b); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3 (C-4′), 153.6 (C-3″ and C-5″), 137.9 (C-2 and C-4″), 133.1 (C-5), 132.0 (C-1″), 129.6 (C-2′ and C-6′), 126.8 (C-4), 121.5 (C-1′), 114.0 (C-3′ and C-5′), 103.3 (C-2″ and C-6″), 61.0 (OMe_c), 56.3 (OMe_b), 55.3 (OMe_a); IR (KBr) ν_{max} 2940, 1596, 1504, 1244, 1177, 1027, 807 cm^{-1}; EI-MS *m/z* 341 (22), 340 (100), 325 (17), 298 (9), 282 (10), 267 (5), 255 (4), 207 (5), 154 (5). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92: Found: C, 66.94; H, 5.81.



3h

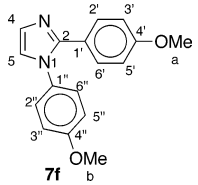
1-(3,4,5-Trimethoxyphenyl)-5-(1-naphthyl)-1*H*-imidazole (3i). The crude reaction product, which was obtained in entry 13 of Table 2 by palladium-catalyzed reaction of **1c** with **2h**, was purified by MPLC on silica gel with a mixture of EtOAc and toluene (90:10 + 0.1% Et_3N) as eluent to give **3i** (0.20 g, 55%) as a pale yellow solid: mp 132−133 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (br s, 1H, H-2), 7.87 (d, J = 8.1 Hz, 1H, H-8′), 7.86 (d, J = 8.0 Hz, 1H, H-5′), 7.76 (d, J = 8.3 Hz, 1H, H-4′), 7.48 (m, 1H, H-6′), 7.43 (m, 2H, H-7′ and H-3′), 7.38 (br s, 1H, H-4), 7.34 (dd, J = 7.1 and 1.2 Hz, 1H, H-2′), 6.27 (s, 2H, H-2″ and H-6″), 3.73 (s, 3H, OMe_b), 3.47 (s, 3H, OMe_a); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.3 (C-4″), 137.6 (C-3″ and C-5″), 137.1 (C-2), 133.4 (C-9′), 132.8 (C-10′), 131.5 (C-1″), 131.1 (C-5), 129.5 (C-8′ and C-2′), 128.4 (C-5′), 128.3 (C-4), 126.9 (C-3′), 126.4 (C-1′), 126.3 (C-6′), 125.3 (C-4′), 125.1 (C-7′), 102 0.2 (C-2″ and C-6”), 60.9 (OMe_b), 56.0 (OMe_a); IR (KBr) ν_{max} 2937, 1601, 1508, 1242, 1125, 1102, 77 cm^{-1}; EI-MS *m/z* 361 (25), 360 (100), 345 (26), 317 (4), 287 (4), 166 (7), 151 (6). Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59. Found: C, 73.19; H, 5.63.



3j

The characterization of all the other 1,5-diaryl-1*H*-imidazoles prepared in this study can be found in the Supporting Information.

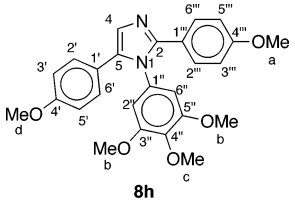
1,2-Bis(4-methoxyphenyl)-1*H*-imidazole (7f). Compound **7f**, which was obtained as a byproduct in the reactions corresponding to entries 8 and 9 of Table 2, was synthesized according to the following procedure. To a flame-dried reaction vessel were added **1b** (0.17 g, 1.0 mmol), **2a** (0.47 g, 2.0 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), CuI (0.38 g, 2.0 mmol), and CsF (0.30 g, 2.0 mmol). The reaction vessel was fitted with a silicon septum, evacuated, and back-filled with argon, and this sequence was repeated twice. DMF (5 mL) was then added under a stream of argon by syringe at room temperature, and the resulting mixture was stirred under argon at 140 °C for 20 h. After this period of time, GLC and GLC−MS analyses of a sample of the reaction mixture, which was treated with a saturated aqueous NH_4Cl solution and extracted with AcOEt, showed that the reaction was complete and the reaction mixture contained compounds **3f**, **7f**, and **8f** in a ca. 3:78:19 molar ratio, respectively. Thus, it was cooled to room temperature, diluted with AcOEt, and poured into a saturated aqueous NH_4Cl solution, and the resulting mixture was stirred in the open air for 0.5 h. It was then extracted with AcOEt, and the organic extract was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **7f** (95 mg, 34%) as a white solid: mp 107−109 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 8.3 Hz, 2H, H-2′ and H-6′), 7.28 (br s, 1H, H-4), 7.16 (m, 2H, H-2″ and H-6″), 7.10 (br s, 1H, H-5), 6.93 (m, 2H, H-3″ and H-5″), 6.81 (d, J = 8.3 Hz, 2H, H-3′ and H-5′), 3.85 (s, 3H, OMe_b), 3.79 (s, 3H, OMe_a); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4 (C-4′), 159.7 (C-4″), 146.3 (C-2), 131.0 (C-1″), 130.2 (C-2′ and C-6′), 127.2 (C-2″ and C-6″), 126.0 (C-4), 122.8 (C-5), 121.0 (C-1′), 114.8 (C-3″ and C-5″), 113.9 (C-3′ and C-5′), 55.6 (OMe_b), 55.3 (OMe_a); IR (KBr) ν_{max} 2962, 1608, 1515, 1502, 1250, 1022, 831 cm^{-1}; EI-MS *m/z* 281 (19), 280 (100), 279 (33), 265 (21), 238 (16), 147 (17). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75. Found: C, 72.67; H, 5.66.



7f

1-(3,4,5-Trimethoxyphenyl)-2,5-bis(4-methoxyphenyl)-1*H*-imidazole (8h). To a flame-dried reaction vessel were added **1c** (0.23 g, 1.0 mmol), **2a** (0.70 g, 3.0 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), CuI (0.57 g, 3.0 mmol), and CsF (0.46 g, 3.0 mmol). The reaction vessel was fitted with a silicon septum, evacuated, and back-filled with argon, and this sequence was repeated twice. DMF (5 mL) and P(*t*-Bu)$_3$ (50 μL, 0.2 mmol) were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was heated to 140 °C under argon with stirring and maintained at this temperature for 114 h. GLC and GLC−MS analyses of

a sample of the reaction mixture, which was treated with a saturated aqueous NH_4Cl solution and extracted with AcOEt, showed the presence of two new compounds in a ca. 1:1 molar ratio and of unreacted **1c** and **2a**. However, the conversion of the reaction did not significantly increase after further stirring for 12 h at 140 °C. Thus, the reaction mixture was cooled to room temperature, diluted with AcOEt, and poured into a saturated aqueous NH_4Cl solution. The resulting mixture was stirred in the open air for 0.5 h and extracted with AcOEt. The organic extract was washed with brine, dried, and concentrated under reduced pressure, and the residue was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **6h** (94 mg, 21%) as a white solid: mp 129−131 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (m, 2H, H-2″ and H-6″), 7.29 (br s, 1H, H-4), 7.04 (m, 2H, H-2′ and H-6′), 6.81 (m, 2H, H-3″ and H-5″), 6.80 (m, 2H, H-3′ and H-5′), 6.29 (m, 2H, H-2″ and H-6″), 3.88 (s, 3H, OMe_c), 3.79 (s, 3H, OMe_a), 3.78 (s, 3H, OMe_d), 3.60 (s, 3H, OMe_b); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.1 (C-4″). 159.3 (C-4′), 153.6 (C-3″ and C-5″), 146.9 (C-2), 138.3 (C-4″), 134.6 (C-5), 132.1 (C-1″), 130.1 (C-2″ and C-6″), 129.8 (C-2′ and C-6′), 125.2 (C-4), 121.6 (C-1′ and C-1″), 113.9 (C-3″ and C-5″), 113.8 (C-3′ and C-5′), 105.9 (C-2″ and C-6″), 61.2 (OMe_c), 56.3 (OMe_b), 55.3 (OMe_d and OMe_a); IR (Kbr) ν_{max} 2940, 1595, 1499, 1246, 1128, 1029, 840 cm^{-1}; EI-MS *m/z* 447 (28), 446 (100), 431 (11), 298 (4), 271 (5), 223 (4), 133 (4). Anal. Calcd for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.87. Found: C, 69.77; H, 5.75.



8h

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Supporting Information Available: Experimental procedures, characterization for compounds **1b**−**f** and **3b**−**d**,**f**,**j**,**l**,**m** and ^{1}H and ^{13}C data for compounds **7a** and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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