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Regiocontrolled Synthesis of 1,2-Diaryl-1*H*-imidazoles by Palladium- and Copper-Mediated Direct Coupling of 1-Aryl-1*H*-imidazoles with Aryl Halides under Ligandless Conditions

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A large variety of 1,2-diaryl-1*H*-imidazoles, including a selective COX-2 inhibitor, have been regioselectively synthesised in moderate to high yields by direct coupling of 1-aryl-1*H*-imidazoles with aryl iodides or bromides in DMF in the presence of CsF and catalytic amounts of $Pd(OAc)_2$ under ligandless conditions. A possible mechanism for this new highly regioselective C-2 arylation reaction, involving the formation of an organocopper(I) derivatives followed by a transmetallation reaction with an arylpalladium(II) halide species and a reductive elimination, is proposed. New one-step procedures for the synthesis of 1,2,5-triaryl-1*H*-imidazoles, based on palladium- and copper-mediated arylation of 1-aryl-1*H*-imidazoles, have also been developed. Interestingly, some imidazole derivatives prepared in this study have been found to exhibit significant cytotoxic activity against some human tumour cell lines.

Introduction

Imidazoles possessing two aryl substituents appear frequently in molecules that elicit important biological responses. Thus, some 1,5-diaryl-1*H*-imidazoles **1** (Figure 1) include substances that act as selective inhibitors of cyclooxygenase-2 (COX-2)[1] and are cytotoxic against a variety of human cancer cell lines.[2] On the other hand, some 1,2-diaryl-1*H*-imidazoles **2** have been reported to be antagonists of the cannabinoid CB_1 receptor[3,4] or to be able to inhibit COX-2 selectively.[5,6,7] The biological activities of compounds **1** and **2** have made them popular synthetic targets, and numerous methods for the synthesis of these heterocycles have been developed.[8,9] These synthetic methods, however, involve the construction of the imidazole ring by multi-step reaction sequences and, before our studies, no simple and straightforward synthesis of compounds **1** and **2** had been described, with the exception of that of compound **2m**, which was recently prepared in 31% yield by Cu^I-mediated *N*-arylation of **3b** with 4-nitrophenyl iodide (**4h**).[8f]

We have recently been directing attention to the regioselective synthesis of these heterocycles by transition metal-mediated direct *C*-arylation of readily available 1-aryl-1*H*-imidazoles **3**[10] and have found that a variety of compounds **1** (R^1 = H) can be regioselectively synthesised, generally in moderate yields, through direct coupling of the corresponding 1-substituted derivatives with aryl halides **4** in DMF at 140 °C in the presence of CsF as the base and a catalyst precursor consisting of a mixture of $Pd(OAc)_2$ and $AsPh_3$ (Scheme 1).[2]

The obtained data supported a reaction mechanism involving electrophilic attack of an arylpalladium(II) halide species onto the most electron-rich position in the imidazole ring of a given compound **3** (see Figure 4 below).[2] Moreover, it was found that, among the imidazoles synthesised in this study, compounds **1b**, **1c**, **1d** and **3b** were characterised by significant cytotoxicity against human tumour cell lines, **1b** being the most potent compound [MG-MID log GI_{50} = –7.09].[2]

These results stimulated our interest in developing a simple, efficient and general method for the regioselective synthesis of 1,2-diaryl-1*H*-imidazoles **2**, involving the transition metal-mediated direct C-2 arylation of compounds **3** with aryl halides **4**, and in evaluating the cytotoxic activities of some imidazole derivatives prepared in this way. On the other hand, Miura and co-workers[11] had previously synthesised 1-methyl-2-phenyl-*1H*-imidazole (**7**) in modest

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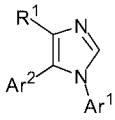
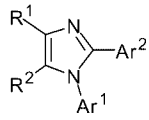
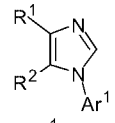


1a: R^1 = H; Ar^1 = Ar^2 = C_6H_5
1b: R^1 = H; Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 4-$MeOC_6H_4$
1c: R^1 = H; Ar^1 = Ar^2 = 4-$MeOC_6H_4$
1d: R^1 = H; Ar^1 = C_6H_5; Ar^2 = 4-$CF_3C_6H_4$
1e: R^1 = H; Ar^1 = C_6H_5; Ar^2 = 4-$MeOC_6H_4$
1f: R^1 = H; Ar^1 = 4-$MeOC_6H_4$; Ar^2 = 3,4,5-$(MeO)_3C_6H_2$
1g: R^1 = H; Ar^1 = 4-$MeSO_2C_6H_4$; Ar^2 = 3,4,5-$(MeO)_3C_6H_2$
1h: R^1 = H; Ar^1 = 4-$MeSO_2C_6H_4$; Ar^2 = 4-$MeOC_6H_4$
1i: R^1 = H; Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 2-naphthyl
1j: R^1 = H; Ar^1 = 2-naphthyl; Ar^2 = 3,4,5-$(MeO)_3C_6H_2$



2a: R^1 = R^2 = H; Ar^1 = Ar^2 = C_6H_5
2b: R^1 = R^2 = H; Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 4-$MeOC_6H_4$
2c: R^1 = R^2 = H; Ar^1 = Ar^2 = 4-$MeOC_6H_4$
2d: R^1 = R^2 = H; Ar^1 = C_6H_5; Ar^2 = 4-$CF_3C_6H_4$
2e: R^1 = R^2 = H; Ar^1 = C_6H_5; Ar^2 = 4-$MeOC_6H_4$
2f: R^1 = R^2 = H; Ar^1 = 4-$MeOC_6H_4$; Ar^2 = 3,4,5-$(MeO)_3C_6H_2$
2g: R^1 = R^2 = H; Ar^1 = 4-$MeSO_2C_6H_4$; Ar^2 = 3,4,5-$(MeO)_3C_6H_2$
2h: R^1 = R^2 = H; Ar^1 = 4-$MeSO_2C_6H_4$; Ar^2 = 4-$MeOC_6H_4$
2i: R^1 = R^2 = H; Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 2-naphthyl
2j: R^1 = R^2 = H; Ar^1 = 2-naphthyl; Ar^2 = 3,4,5-$(MeO)_3C_6H_2$
2k: R^1 = Me; R^2 = H; Ar^1 = 4-$MeSO_2C_6H_4$; Ar^2 = 4-ClC_6H_4
2l: R^1 = R^2 = Cl; Ar^1 = 4-$MeSO_2C_6H_4$; Ar^2 = 4-$MeOC_6H_4$
2m: R^1 = R^2 = H; Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 4-$NO_2C_6H_4$

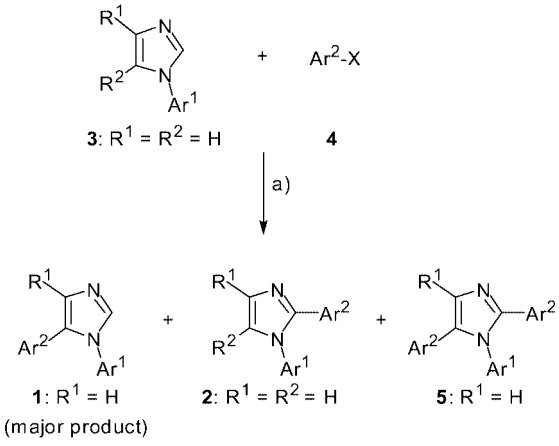


3a: R^1 = R^2 = H; Ar^1 = C_6H_5
3b: R^1 = R^2 = H; Ar^1 = 3,4,5-$(MeO)_3C_6H_2$
3c: R^1 = R^2 = H; Ar^1 = 4-$MeOC_6H_4$
3d: R^1 = R^2 = H; Ar^1 = 4-$MeSO_2C_6H_4$
3e: R^1 = R^2 = H; Ar^1 = 2-naphthyl
3f: R^1 = Me; R^2 = H; Ar^1 = 4-$MeSO_2C_6H_4$
3g: R^1 = R^2 = Cl; Ar^1 = 4-$MeSO_2C_6H_4$
3h: R^1 = H; R^2 = Me; Ar^1 = 4-$MeSO_2C_6H_4$

Ar^2–X

4a: Ar^2 = C_6H_5; X = I
4b: Ar^2 = 4-$MeOC_6H_4$; X = I
4c: Ar^2 = 4-$CF_3C_6H_4$; X = I
4d: Ar^2 = 3,4,5-$(MeO)_3C_6H_2$; X = I
4e: Ar^2 = 4-ClC_6H_4; X = I
4f: Ar^2 = 2-naphthyl; X = Br
4g: Ar^2 = 4-$MeSO_2C_6H_4$; X = F
4h: Ar^2 = 4-$NO_2C_6H_4$; X = I

Figure 1. Chemical structures of compounds **1**–**4**.



Scheme 1.[2] Reagents and conditions: a) **4** (2.0 equiv.), $Pd(OAc)_2$ (5 mol-%), $AsPh_3$ (10 mol-%), CsF (2.0 equiv.), DMF, 140 °C, 17–161 h, 9–61%.

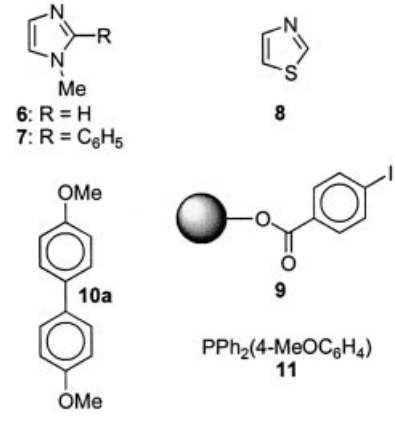


Figure 2. Chemical structures of compounds **6**–**9**, **10a**, **11**.

yield by Pd- and Cu-mediated treatment of 1-methyl-1*H*-imidazole (**6**, Figure 2) with iodide **4a**, but we were aware of the fact that, under suitable experimental conditions, **6** and thiazole (**8**) can undergo efficient Pd- and Cu-mediated arylation at C-2 with iodobenzoate immobilized on an insoluble polymer support **9**[12] or iodide **4b**,[13] respectively.

In this paper we report the results of our study[14] of the Pd- and Cu-mediated C-2 arylation of 1-aryl-1*H*-imidazoles **3** with aryl halides **4** and disclose an efficient procedure for the highly regioselective synthesis of various diaryl-1*H*-imidazoles **2**, involving significant modifications, in terms of Pd catalyst precursor and the base, of the experimental conditions used by Miura and co-workers for the synthesis of **7** from **6**[11] and by Kondo and co-workers[12] and Mori and co-workers[13] for the C-2 arylation of **6** and **8**. More-

over, we also describe new one-step procedures for the preparation of some 1,2,5-triaryl-1*H*-imidazoles **5** obtained as by-products in the Pd- and Cu-mediated synthesis of some compounds **2**.[15] Finally, we report data that indicate that some imidazoles prepared in this study exhibit an indisputable cytotoxicity against human tumour cell lines.

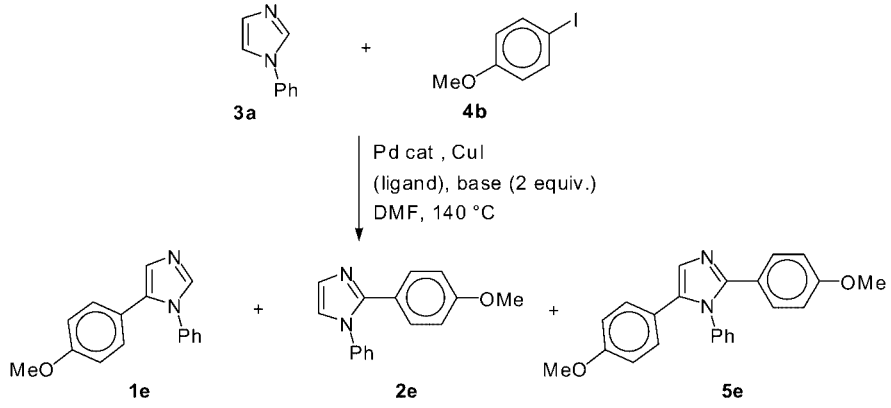
Results and Discussion

We initiated the study on the synthesis of compounds **2** by performing the reaction between **3a** and **4b** under the experimental conditions used by Miura and co-workers for the synthesis of **6**.[11] Thus, **3a** was treated with 2 equiv. of **4b**, 2 equiv. of CuI and 2 equiv. of Cs_2CO_3 in DMF at 140 °C for 48 h in the presence of 10 mol-% $Pd(OAc)_2$ and 20 mol-% PPh_3 (Table 1, Entry 1). This reaction took place with 87% conversion and furnished a complex reaction mixture containing triarylated imidazole **5e** as the major product, diaryl imidazole **1e**,[2] significant amounts of **1a** and **2a** and (4-methoxyphenyl)diphenylphosphane (**11**), in addition to the required diaryl imidazole **2e**,[2] which was obtained in 9% GLC yield. It should be noted that compounds **1a**, **2e**, **5e**, **10a** and **11** were also by-products of the reaction between **3a** and **4b** in the presence of Cs_2CO_3 as the base and a catalyst precursor consisting of a mixture of $Pd(OAc)_2$ and PPh_3, which produces **1e** as the major product.[2] Compounds **1a** and **2a** were presumably derived from arylation reactions between **3a** and iodide **4a**, produced by an unexpected exchange reaction involving PPh_3 and **4b**.

In a search for a more selective and efficient procedure for the synthesis of **2e** we carefully examined the influence on the reaction of a number of variables, such as the amount of Pd, the Pd ligand, the **3a**/CuI molar ratio and the base (Table 1).

We thus found that CuI, even in the absence of $Pd(OAc)_2$, is able to promote the C-2 arylation of **3a** with complete regioselectivity. However, the yields were generally low (Table 1, Entries 2, 3 and 11). Moreover, we observed that the use of arylated ligands (e.g., PPh_3 or $AsPh_3$) gave rise to by-products originating from the scrambling of the organic groups of the ligands with the aryl moiety of **4b** (Table 1, Entries 1–3 and 5), but the use of ligands that did not contain aryl groups did not allow us to improve the yield of the reaction significantly (Table 1, Entries 4 and 6). Nevertheless, we found that, under ligandless conditions, catalytic amounts of $Pd(OAc)_2$ promote the regioselective C-2 arylation of compound **3a** in the presence of 2 equiv. of CuI and 2 equiv. of Cs_2CO_3 or CsF (Table 1, Entries 7 and 8). Moreover, the use of CsF as the base allowed us to obtain homogeneous reaction mixtures, higher yields and more reproducible results. Finally, we found that when the

Table 1. Screening reaction conditions for the selective C–2 arylation of **3a** with iodide **4b**.



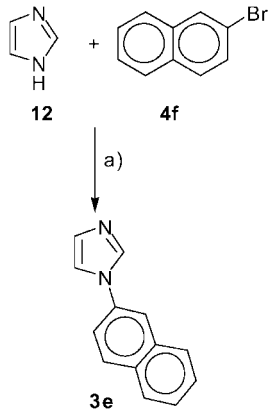
Entry[a]	$Pd(OAc)_2$ (mol-%)	CuI (equiv.)	Ligand (mol-%)	Base	GLC conversion of **3a**[b]	**2e**:**1e**:**5e** GLC molar ratio	Yield of **2e**[b,c]
1	10	2.0	PPh_3 (20)	Cs_2CO_3	88	15:8:77	9[d]
2	–	2.0	PPh_3 (65)	Cs_2CO_3	65	100:0:0	19[d]
3	–	2.0	PPh_3 (20)	Cs_2CO_3	85	100:0:0	30[d]
4	10	2.0	$P(OEt)_3$ (20)	Cs_2CO_3	87	68:24:8	20
5	10	2.0	$AsPh_3$ (20)	Cs_2CO_3	88	44:25:31	30[d]
6	10	2.0	$P(tBu)_3$ (20)	Cs_2CO_3	90	24:18:58	21
7	10	2.0	–	Cs_2CO_3	100	44:12:44	42
8	10	2.0	–	CsF	97	54:6:40	50 (41)
9	10	0.5	–	CsF	40	35:65:0	11
10	5	2.0	–	CsF	100	81:1:18	(62)
11	–	2.0	–	CsF	44	100:0:0	26

[a] The reactions were performed with 1 mmol of **3a**, 2 equiv. of **4b**, 2 equiv. of base 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 values in parenthesis indicate isolated yields. [d] The crude reaction mixture also contained significant amounts of 1,2- and 1,5-diphenyl-1*H*-imidazole **2a** and **1a**, respectively.

amount of $Pd(OAc)_2$ was reduced from 10 mol-% to 5 mol-% the reaction occurred with higher regioselectivity and in better chemical yield (compare Entries 8 and 10 of Table 1). In contrast, unsatisfactory results were obtained when we reduced the amount of CuI from 2.0 to 0.5 equiv.; in this case, in fact, the prevalent formation of the regioisomeric 1,5-diaryl-1*H*-imidazole **1e** was observed (compare Entries 8 and 9 of Table 1).

After this initial screening, which had demonstrated the viability of the Pd- and Cu-mediated selective C-2 arylation of **3a** with **4b**, we tested the scope and limitations of this reaction by applying the reaction conditions of Entry 10 of Table 1 to the synthesis of 1,2-diaryl-1*H*-imidazoles **2** from 1-aryl-1*H*-imidazoles **3a**–**g** and aryl halides **4a**–**f**.

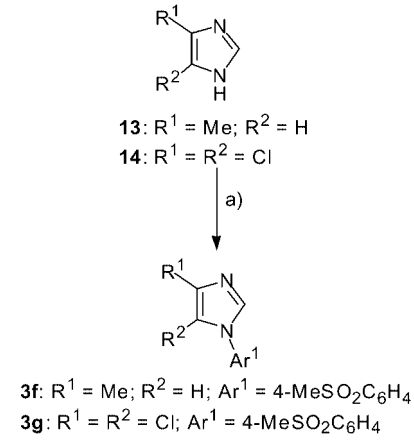
Compounds **3a**–**d** were prepared as previously reported,[2] whilst **3e** was synthesised by the method described in 1999 by Buchwald et al.[10i] [i.e., by treatment of 2-bromonaphthalene (**4f**) with 1.5 equiv. of imidazole (**12**) in xylenes at 110 °C in the presence of Cs_2CO_3, 1,10-phenanthroline and catalytic amounts of *trans*-*trans*-dibenzylideneacetone (dba) and $(CuOTf)_2$·toluene (Scheme 2)].



Scheme 2. Reaction conditions: a) **12** (1.5 equiv.), $(CuOTf)_2$·toluene (5 mol-%), dba (5 mol-%), 1,10-phenanthroline (1.0 equiv.), Cs_2CO_3 (1.1 equiv.), xylenes, 110 °C, 71 h, 61%.

On the other hand, compounds **3f** and **3g** were synthesised by treatment of **13** and **14**, respectively, with NaH in DMF, followed by treatment with fluoride **4g** (Scheme 3). Nevertheless, **3f** prepared in this way was not regiochemically pure: in fact, GLC, EI-MS and NMR analyses showed that the reaction illustrated in Scheme 3 furnished a 75:25 mixture of **3f** and 5-methyl-1-[(4-methylsulfonyl)-phenyl]-1*H*-imidazole (**3h**). We then used this mixture in a subsequent Pd- and Cu-mediated arylation reaction with iodide **4e**.

Table 2 summarises the results of the reactions performed to prepare 1,2-diaryl-1*H*-imidazoles **2a**–**l**. As illustrated in this Table, the established procedure allowed us to obtain compounds **2a**–**k** in moderate to high yields and with high or complete selectivity (Table 2, Entries 1–7 and 9–12). In particular, as regards the selectivity, all of the reactions performed in the presence of 5 mol-% $Pd(OAc)_2$, 2 equiv. of CuI and 2 equiv. of CsF provided reaction mixtures in which 1,5-diaryl-1*H*-imidazoles **1a**–**j** were either present only in very small amounts or completely absent. However, significant amounts of 1,2,5-triaryl-1*H*-imidazoles **5a**, **5b**, **5c**, **5d** and **5e** contaminated the reaction mixtures obtained in Entries 1, 11, 10, 2 and 9, respectively, of Table 2. Compounds **5a** and **5e** were isolated in 26% and 16% yields, respectively, from the reaction mixtures of Entries 1 and 9 of Table 2. On the other hand, compound **5d** was identified by comparison of its GLC retention time and EI-MS spectrum with those of an authentic sample of this substance obtained as a by-product in the Pd-catalysed C–5 arylation of **3a** with **4c**.[2]

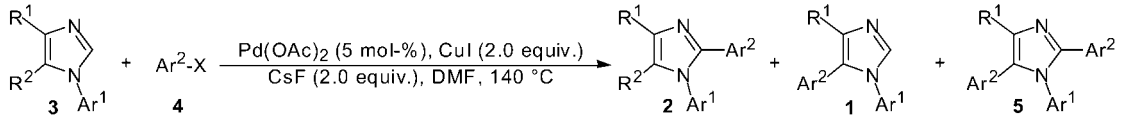


Scheme 3. Reaction conditions: a) NaH (1.03 equiv.), DMF, 0–20 °C, 2 h, then **4g** (1.03 equiv.), DMF, room temp., 24 h (for **3f**) or 50 °C, 67 h (for **3g**), 75% for **3f**, 78% for **3g**.

Interestingly, compound **2k**, a selective COX-2 inhibitor,[5] could be prepared in 62% yield from **3f** and **4e** by the established procedure (Table 2, Entry 12), so this synthesis of **2k** competes favourably with those reported in the literature for the preparation of this and similar compounds,[5] which provide the required substances by multi-step sequences and in lower overall yields.[5]

The structural assignments of compounds **2a**–**l**, **5a** and **5e** (Figure 3) were achieved with the aid of their ^1H and ^{13}C NMR spectra and by a combination of 2D NMR techniques including ^1H–^{13}C Heteronuclear Multiple Bond Correlation (HMBC) and ^1H–^{13}C Heteronuclear Single Quantum Coherence (HSQC). On the other hand, the structures of 1,5-diaryl-1*H*-imidazoles **1e** and **1f**, which were by-products of the reactions corresponding to Entries 9 and 3 of Table 2, were established by comparison of the GLC retention times and EI-MS spectra of these imidazoles with those of authentic samples obtained by direct Pd-catalysed coupling of the corresponding 1-aryl-1*H*-imidazoles **3** with the appropriate aryl halides **4** in DMF at 140 °C by the procedure we developed recently.[2] Finally, the structural assignments of **5b** and **5c**, which we had preliminarily made on the basis of EI-MS spectra of these compounds, were confirmed by comparison of their EI-MS data and GLC retention time with those of authentic samples of **5b** and **5c** prepared as previously reported[2] by treat-

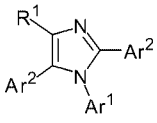
Table 2. Pd- and Cu-mediated synthesis of 1,2-diaryl-1*H*-imidazoles **2** from 1-aryl-1*H*-imidazoles **3** and aryl halides **4**.



Entry[a]	Reagents 3	R^1	R^2	Ar^1	4	Ar^2	X	Reaction time (h)	Products 2:1:5 GLC molar ratio	2	Isolated yield (%)
1	**3a**	H	H	C_6H_5	**4a**	C_6H_5	I	65	63:0:37	**2a**	55[b]
2	**3a**	H	H	C_6H_5	**4c**	4-$CF_3C_6H_4$	I	64	72:0:28	**2d**	64
3	**3c**	H	H	4-$MeOC_6H_4$	**4d**	3,4,5-$(MeO)_3C_6H_2$	I	24	96:4:0	**2f**	59
4	**3d**	H	H	4-$MeSO_2C_6H_4$	**4d**	3,4,5-$(MeO)_3C_6H_2$	I	20	100:0:0	**2g**	79
5	**3d**	H	H	4-$MeSO_2C_6H_4$	**4b**	4-$MeOC_6H_4$	I	20	100:0:0	**2h**	67
6	**3b**	H	H	3,4,5-$(MeO)_3C_6H_2$	**4f**	2-naphthyl	Br	43	100:0:0	**2i**	57
7	**3e**	H	H	2-naphthyl	**4d**	3,4,5-$(MeO)_3C_6H_2$	I	42	100:0:0	**2j**	57
8	**3g**	Cl	Cl	4-$MeSO_2C_6H_4$	**4b**	4-$MeOC_6H_4$	I	19	–	**2l**	94
9	**3a**	H	H	C_6H_5	**4b**	4-$MeOC_6H_4$	I	48	81:1:18	**2e**	62[c]
10	**3c**	H	H	4-$MeOC_6H_4$	**4b**	4-$MeOC_6H_4$	I	20	87:0:13	**2c**	38
11	**3b**	H	H	3,4,5-$(MeO)_3C_6H_2$	**4b**	4-$MeOC_6H_4$	I	48	86:0:14	**2b**	52
12	**3f**[d]	Me	H	$MeSO_2C_6H_4$	**4e**	4-ClC_6H_4	I	26	90:0:10	**2k**	62

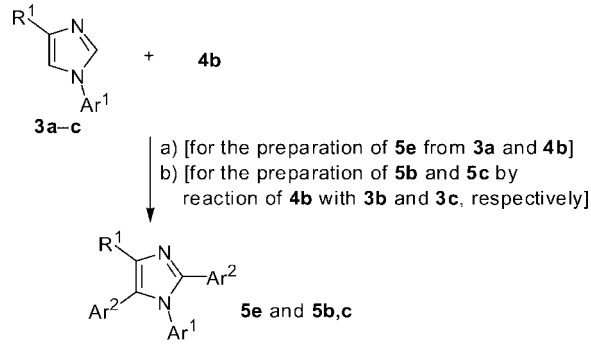
[a] The reactions were run with 1 mmol of a particular compound **3**, 2 equiv. of a given compound **4**, 5 mol-% $Pd(OAc)_2$, 2 equiv. of CuI and 2 equiv. of CsF in DMF at 140 °C until the conversions were quantitative. [b] MPLC of the crude reaction mixture on silica gel after conventional workup also allowed isolation of **5a** in 26% yield. [c] MPLC of the crude reaction mixture on silica gel after conventional workup also allowed isolation of **5e** in 16% yield. [d] Used as a 75:25 mixture with 5-methyl-1-[(4-methylsulfonyl)phenyl]-1*H*-imidazole (**3h**).

ment of 3 equiv. of **4b** with **3b** and **3c**, respectively, in DMF at 140 °C for 114 h in the presence of 10 mol-% $Pd(OAc)_2$, 20 mol-% P(*t*Bu)$_3$, 3 equiv. of CuI, and 3 equiv. of CsF (Scheme 4). We then used a similar procedure to prepare **5e** in 32% yield from **3a** and **4b** (Scheme 4).



5a: R^1 = H; Ar^1 = Ar^2 = C_6H_5
5b: R^1 = H; Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 4-$MeOC_6H_4$
5c: R^1 = H; Ar^1 = Ar^2 = 4-$MeOC_6H_4$
5d: R^1 = H; Ar^1 = C_6H_5; Ar^2 = 4-$CF_3C_6H_4$
5e: R^1 = H; Ar^1 = C_6H_5; Ar^2 = 4-$MeOC_6H_4$

Figure 3. Chemical structures of compounds **5a**–**e**.

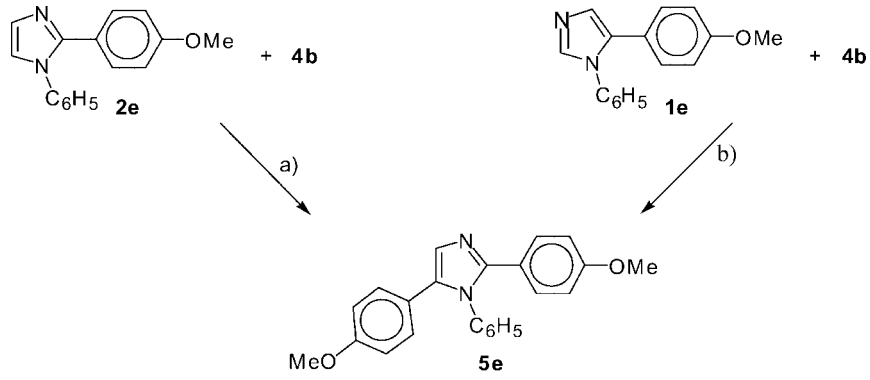


Scheme 4. Reaction conditions: a) **4b** (2.0 equiv.), $Pd(OAc)_2$ (10 mol-%), Cs_2CO_3 (2.0 equiv.), CuI (2.0 equiv.), DMF, 140 °C, 66 h, 32%. b) **4b** (3.0 equiv.), $Pd(OAc)_2$ (10 mol-%), P(*t*Bu)$_3$ (20 mol-%) (for **3b**), $[P(tBu)_3H]^+BF_4^-$ (20 mol-%) (for **3c**), CsF (3.0 equiv.), CuI (3.0 equiv.), DMF, 140 °C, 114–281 h, 21% (for **5b**), 36% (for **5c**).

Finally, we found that compound **5e**, which we had isolated in 16% yield as a by-product of the Pd- and Cu-mediated reaction between **3a** and **4b** (Table 2, Entry 9), could also be prepared in 57% GLC yield by treatment of **2e** with 2 equiv. of **4b** in DMF at 140 °C in the presence of 5 mol-% $Pd(OAc)_2$, 2 equiv. of CuI and 2 equiv. of CsF (Scheme 5). On the other hand, **5e** could also be obtained in 74% GLC yield from the reaction between **2e** and 2 equiv. of **4b** in DMF at 140 °C for 46 h in the presence of 5 mol-% $Pd(OAc)_2$, 2 equiv. of CuI and 2 equiv. of CsF, which took place with quantitative conversion (Scheme 5).

These results suggest that 1,2,5-trisubstituted 1*H*-imidazoles **5**, which were present in several crude reaction mixtures obtained from the Pd- and Cu-mediated arylation reactions of 1-aryl-1*H*-imidazoles **3**, are very probably mainly formed by Pd- and Cu-mediated arylation of 1,5-diaryl-1*H*-imidazoles **2**, even though the presence of these last compounds has rarely been observed in the crude final reaction mixtures from the Pd- and Cu-mediated reactions. On the other hand, the results of the reactions summarised in Scheme 5 show that the rate of a Pd- and Cu-mediated arylation of a typical 1,5-diaryl-1*H*-imidazole is higher than that of a Pd- and Cu-mediated reaction involving the corresponding 1,2-diaryl-1*H*-imidazole.

It should also be noted that the success of the selective C-2 arylation of compounds **3** strongly depended on the amount of CuI used. In fact, when the amount of CuI was reduced from 2.0 equiv. to 0.5 equiv., the regioselectivity of the arylation reaction switched from C-2 to C-5 (compare Entries 8 and 9, Table 1). Moreover, we had previously observed that treatment of **3b** with 2.0 equiv. of **4b** in DMF



Scheme 5. a) **4b** (2.0 equiv.), $Pd(OAc)_2$ (5 mol-%), CsF (2.0 equiv.), CuI (2.0 equiv.), DMF, 140 °C, 113 h, 57% (GLC). b) **4b** (2.0 equiv.), $Pd(OAc)_2$ (5 mol-%), CsF (2.0 equiv.), CuI (2.0 equiv.), DMF, 140 °C, 46 h, 74% (GLC).

at 140 °C in the presence of 10 mol-% $Pd(OAc)_2$ and 2 equiv. of Cs_2CO_3 provided a mixture of **1b** and **2b** in a 87:13 molar ratio.[2]

The mechanisms we propose for the Pd- and Cu-mediated C-2 arylation and the Pd-catalysed C-5 regioselective arylation of 1-aryl-1*H*-imidazoles **3** are shown in Figure 4. In particular, we suppose that, in the presence of a base, 1-aryl-1*H*-imidazoles **3** exist in equilibrium with the corresponding organocopper(I) derivatives **B**.[16] This hypothesis is partly supported by literature data concerning the ability of Cu^I salts to metallate acidic C–H bonds and, in particular, the C-2 position of imidazoles **3**.[17] Compounds **B** might then undergo transmetallation with the arylpalladium(II) halide species **A**, which derive from the oxidative addition of aryl halides **4** to the Pd^0 species generated in situ. Finally, subsequent deprotonation and reductive elimination might give the required 1,2-diaryl-1*H*-imidazoles **2**. On the other hand, we suppose that, when the Pd-catalysed arylation reaction of **3** is carried out in the presence of catalytic amounts of Cu^I salts, which are not sufficient to allow the formation of significant amounts of salts **B** from imidazoles **3**, the arylation occur prevalently at C-5 and presumably involves a base-promoted electrophilic attack of complex **A** onto C-5 of the imidazole ring. This position has been reported[18] to be more reactive than C-4 or C-2 in electrophilic substitution reactions when neutral imidazole intermediates are involved. The hypothesis that two competitive mechanisms may operate is also supported by the fact that a higher C-2 selectivity was observed when the amount of $Pd(OAc)_2$ was lowered. Complex **A** should not be involved in the rate-determining step of the C-2 arylation path, but rather involved in that of the C-5 arylation reaction.

The proposed mechanism for the palladium- and copper-mediated C-2 arylation of compounds **3** is also supported by the observed dependence of the reaction time on electronic effects. In fact, for compounds **3** characterised by a strongly electron-withdrawing group such as 4-Me$SO_2C_6H_4$, which should enhance the kinetic acidity of the 2-H proton, these were shorter (19–26 h) than those found for 1-aryl-1*H*-imidazoles containing a strongly electron-rich group such as 3,4,5-$(MeO)_3C_6H_2$ at N-1 (43–48 h). In contrast, the yields did not appear to be affected by the nature of the aryl halides **4**. Nevertheless, at present it seems difficult, on the basis of this mechanism, to explain the complete C-2 regioselectivity of the Pd- and Cu-mediated arylation of 2-aryl-1*H*-imidazoles **3** characterised by a strongly electron-rich group at N-1.

We also believe that the fact that the palladium- and copper-mediated arylation reaction of compounds **3** occurs in the absence of ligands such as triarylphosphanes or $AsPh_3$ can be explained by allowing for the fact that imidazoles **3** probably represent the ligands of the palladium species involved in this reaction.

It is also interesting to note that, according to the mechanisms reported in Figure 4, the C-2 arylation of compounds **3** should involve the use of catalytic amounts of CuI. In fact, this salt, which is initially consumed to form the species **B**, is regenerated in the steps of the reaction that correspond to the conversion of this organocopper species into the transmetallation derivative. Nevertheless, as shown by comparison of Entries 8 and 9 of Table 1, the C-2 arylation reaction requires the use of a large molar excess of CuI, which appears to be necessary in order to cause the formation of significant amounts of **B** and suitable reaction rates.

On the other hand, we believe that the C-2 arylation of **3a** with **4b**, which we carried out in DMF at 140 °C in the presence of a Pd-free system consisting of 2 equiv. of CuI and 2 equiv. of Cs_2CO_3 or CsF (Table 1, Entries 2, 3, and 8), can be regarded as a nucleophilic aromatic substitution assisted by CuI and the base, which proceeds through one of the two alternative oxidative addition/reductive elimination pathways recently proposed by Cristeau et al.[10b] for Cu-catalysed nucleophilic substitution with aromatic halides.

Finally, it is worth mentioning that 1,2-diaryl-1*H*-imidazoles **2b**, **2c** and **2f** and 1,2,5-triaryl-1*H*-imidazole **5b** were evaluated over a 5-log dose range in the NCI's in vitro human disease-oriented tumour cell line screening panel, consisting of 60 human tumour cell lines. Compounds **2b**, **2c** and **2f** were found to be moderately cytotoxic, but **2b**, which had cytotoxicity (MG–MID log GI_{50} = –5.45) lower than that of the corresponding 1,5-diaryl-1*H*-imidazole **1b** (MG–MID log GI_{50} = –6.64)[2] was, however, significantly active against the COLO205, HCC-2998, HCT-116, HCT-15,

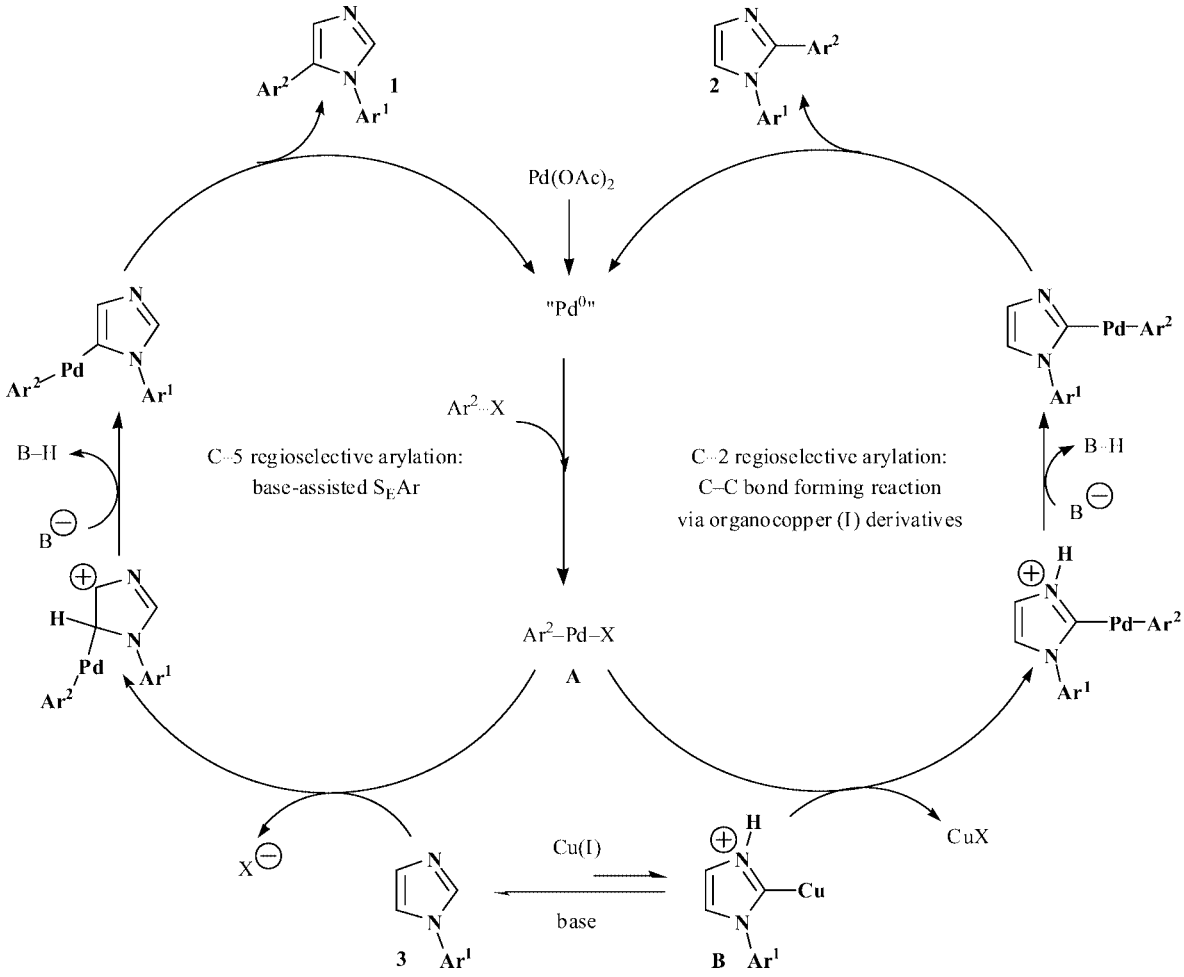


Figure 4. Mechanisms for the Pd- and Cu-mediated C-2 arylation and the Pd-catalysed C-5 arylation of 1-aryl-1*H*-imidazoles **3**.

HT29, KM12 and SW-620 colon cancer cell lines (MG-MID log GI_{50} = –6.33) and the MDA-MB-435 breast cancer line (log GI_{50} = –6.95) of the NCI. On the other hand, **5b** was highly active only against the MOLT-4 leukemia cell line (log GI_{50} = –7.88; log TGI –7.36) and **2c** was also very active against this leukemia cell line (log GI_{50} < –8.00) and the human SR leukemia cell line (log GI_{50} = –7.78).

Conclusions

In this study we have demonstrated that a large variety of 1,2-diaryl-1*H*-imidazoles, including a selective COX-2 inhibitor, can be efficiently and selectively synthesised by direct Pd- and Cu-mediated C-arylation of readily available 1-aryl-1*H*-imidazoles with aryl iodides or bromides. This simple and practical preparation method, which involves the use of experimental conditions very different from those previously employed for the C-2 arylation of 1-methyl-1*H*-imidazole,[11–13] compares favourably with those previously described in the literature, which are based on the construction of the imidazole ring,[9] and allows the preparation of 1,2-diaryl-1*H*-imidazoles containing electron-donating and/or electron-withdrawing substituents on the aryl groups linked at their N-1 and C-2 positions. We have also shown that 1,2,5-triaryl-1*H*-imidazoles can be synthesized by Pd- and Cu-mediated arylation either of 1,2-diaryl-1*H*-imidazoles at their C-5 positions or of 1,5-diaryl-1*H*-imidazoles at their C-2 positions.

It is proposed that the highly regioselective C-2 arylation of 1-aryl-1*H*-imidazoles proceeds by a mechanism involving the formation of an organocopper(I) derivative, followed by a transmetallation with an arylpalladium(II) halide species and by a reductive elimination.

It is also worth noting that some imidazole derivatives synthesised in this study have been found to be significantly cytotoxic against some human tumour cell lines.

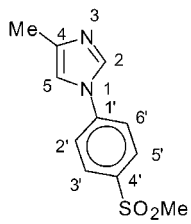
Studies on the application of this highly regioselective C-2 arylation of 1-aryl-1*H*-imidazoles to the synthesis of human CB_1 receptor antagonists related to SR141716[3,19] and constituted of suitably substituted 1,2-diaryl-1*H*-imidazole-4-carboxamide derivatives with methyl, bromo or cyano groups at their C-5 positions are in progress.

Experimental Section

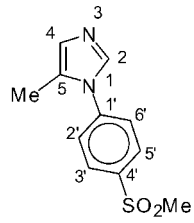
1-(2-Naphthyl)-1*H*-imidazole (3e): Imidazole (**12**, 0.61 g, 9.0 mmol), 1,10-phenanthroline (1.08 g, 6.0 mmol), *trans*,*trans*-dibenzylidene-

acetone (703 mg, 0.30 mmol), Cs_2CO_3 (2.15 g, 6.60 mmol), copper(I) trifluoromethanesulfonate toluene complex (156 mg, 0.30 mmol) and 2-bromonaphthalene (**4f**, 1.24 g, 6.0 mmol) were placed in a flame-dried reaction vessel fitted with a silicon septum. The reaction vessel was evacuated and back-filled with argon in a sequence that was repeated twice. Xylenes (1.2 mL) were then added under a stream of argon and the resulting mixture was stirred under argon at 110 °C for 71 h. It was then cooled to room temperature, diluted with AcOEt (25 mL), poured into a saturated aqueous NaCl solution (30 mL) and extracted with AcOEt (4 × 20 mL). The organic extract was washed with brine (10 mL), dried and concentrated under reduced pressure. The residue was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (96:4) as eluent to give **3e** (0.71 g, 61%) as a pale yellow solid: m.p. 120–121 °C (ref.[20] 121–122 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.98 (br. s, 2 H), 7.93–7.85 (m, 2 H), 7.81 (d, J = 2.2 Hz, 1 H), 7.61–7.49 (m, 3 H), 7.26 (s, 1 H), 7.40 (br. s, 1 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 135.7, 133.4, 132.0, 130.4, 130.0, 127.7 (2 C), 127.3, 126.4 (2 C), 126.4 (2 C), 120.1, 119.0, 118.0 ppm. IR (KBr disk): $\tilde{\nu}$ = 3094, 1599, 1492, 1308, 1058, 814, 759 cm^{-1}. EI–MS: m/z (%) = 195 (15) [M + 1]$^+$, 194 (100) [M]$^+$, 193 (8), 167 (45), 154 (14), 140 (29), 127 (22). The spectral properties of this compound were in satisfactory agreement with those previously reported.[20]

4-Methyl-1-[(4-methylsulfonyl)phenyl]-1*H*-imidazole (3f) and 5-Methyl-1-[(4-methylsulfonyl)phenyl]-1*H*-imidazole (3h): A suspension of NaH in mineral oil (60%, 0.40 g, 10.0 mmol) was washed with pentane (3 mL) and the resultant solid was suspended in DMF (5 mL) and treated under argon with a solution of 4(5)-methyl-1*H*-imidazole (**13**, 0.80 g, 9.80 mmol) in DMF (5 mL). The mixture was stirred for 20 min at room temperature and a solution of 1-fluoro-4-(methylsulfonyl)benzene (**4g**, 1.74 g, 10.0 mmol) in DMF (5 mL) was then added over 4 min. The resulting mixture was stirred at room temperature for 24 h and was then poured into an ice-cooled aqueous NH_4Cl solution (30 mL) and extracted with AcOEt (4 × 25 mL). The organic extract was washed with water (2 × 5 mL), dried and concentrated under reduced pressure. GLC, GLC/EI-MS and NMR analyses of the residue showed the presence of two regioisomeric compounds, **3f** and **3h**, in a 75:25 molar ratio. The residue was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (97:3) as eluent to give a mixture of **3f** and **3h** in a 75:25 molar ratio (1.73 g, 75%) as a colourless solid: m.p. 110–116 °C. ^{1}H NMR (600 MHz, $CDCl_3$): (for **3f**): δ = 8.04 (m, 2 H, 3′-H and 5′-H), 7.92 (br. s, 1 H, 2-H), 7.56 (m, 2 H, 2′-H and 6′-H), 7.08 (br. s, 1 H, 5-H), 3.07 (s, 3 H, SO_2Me), 2.29 (s, 3 H, C-Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): (for **7f**): δ = 141.4 (C-1′), 140.6 (C-4), 138.7 (C-4′), 134.4 (C-2), 129.6 (C-3′ and C-5′), 120.9 (C-2′ and C-6′), 113.9 (C-5), 44.6 (SO_2Me), 13.6 (C-Me) ppm. No NOE cross-peaks between the methyl group at C-4 and the 2′-H and 6′-H protons could be observed. ^{1}H NMR (600 MHz, $CDCl_3$): (for **3h**): δ = 8.09 (m, 2 H, 3′-H and 5′-H), 7.66 (br. s, 1 H, 2-H), 7.52 (m, 2 H, 2′-H and 6′-H), 6.96 (br. s, 1 H, 4-H), 3.10 (s, 3 H, SO_2Me), 2.22 (s, 3 H, C-Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): (for **3h**): δ = 141.0 (C-1′), 140.3 (C-4′), 136.7 (C-2), 129.2 (C-3′ and C-5′), 128.3 (C-4), 127.7 (C-5), 126.0 (C-2′ and C-6′), 44.5 (SO_2Me), 10.0 (C-Me) ppm. A NOE cross-peak between the methyl group at C-5 and the 2′-H and 6′-H protons could be observed. IR (KBr disk): $\tilde{\nu}$ = 3020, 1600, 1514, 1306, 1152, 965, 781 cm^{-1}. EI-MS: m/z (%) (for **3f**) = 237 (15), 236 (100), 235 (35), 157 (29), 130 (21), 116 (13), 103 (7). EI-MS: m/z (%) (for **3h**) = 237 (14) [M + 1]$^+$, 236 (100) [M]$^+$, 235 (28), 157 (21), 130 (20), 116 (9), 103 (6). $C_{11}H_{12}N_2O_2S$ (236.29): calcd. C 55.91, H 5.12; found C 55.87, H 5.08.



3f



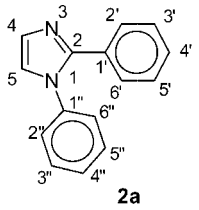
3h

4,5-Dichloro-1-[(4-methylsulfonyl)phenyl]-1*H*-imidazole (3g): The crude product obtained from the reaction carried out at 50 °C for 67 h between **4g** (1.39 g, 8.0 mmol) and a DMF solution of the sodium salt prepared from 4,5-dichloro-1*H*-imidazole (**14**, 1.07 g, 7.8 mmol) by the procedure used for the synthesis of a mixture of **3f** and **3h** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (97:3) as eluent to give **3g** (1.77 g, 78%) as a pale yellow solid: m.p. 150–151 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.15 (m, 2 H), 7.64 (m, 2 H), 7.63 (s, 1 H), 3.14 (s, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 141.3, 138.7, 134.3, 129.2 (2 C), 128.6, 126.0 (2 C), 113.7, 44.4 ppm. IR (KBr disk): $\tilde{\nu}$ = 3121, 1594, 1500, 1307, 1148, 949 cm^{-1}. EI-MS: m/z (%) = 292 (69) [M + 1]$^+$, 290 (100) [M], 213 (18), 211 (28), 176 (20), 150 (13), 108 (21). $C_{10}H_8Cl_2N_2O_2S$ (291.16): calcd. C 41.25, H 2.77; found C 41.13, H 2.55.

General Procedure for the Pd- and Cu-Mediated Synthesis of 1,2-Diaryl-1*H*-imidazoles 5 from Compounds 3 and Aryl Halides 4: The appropriate compound **3** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), CuI (0.38 g, 2.0 mmol), CsF (0.30 g, 2.0 mmol) and (if a solid) the aryl iodide or bromide **4** (2.0 mmol) were placed in a flame-dried reaction vessel. The reaction vessel was fitted with a silicon septum and then evacuated and back-filled with argon in a sequence that was repeated twice. DMF (5 mL) and (if a liquid) the aryl iodide or bromide (2.0 mmol) were then added successively by syringe at room temperature under a stream of argon. The resulting mixture was stirred at 140 °C under argon for the period of time given in Table 2. The degree of completion of the reaction and the composition of the reaction mixture were established by GLC and GLC-MS analyses of a sample of the crude reaction mixture after it had been treated with a saturated aqueous NH_4Cl solution and extracted with AcOEt. After being cooled to room temperature, the reaction mixture was diluted with AcOEt (35 mL) and poured into a saturated aqueous NH_4Cl solution (75 mL), and the resulting mixture was stirred in the open air for 0.5 h and then extracted with AcOEt (4 × 50 mL). The organic extract was washed with water (2 × 5 mL), dried and concentrated under reduced pressure and the residue was purified by MPLC on silica gel. The chromatographic fractions containing the required compound were collected and concentrated. A CH_2Cl_2 solution of the residue was then stirred for 2 h at room temp. with 3-(mercapto)propyl-functionalised silica gel (0.50 g, loading 1.2 mmol g^{-1}), which was used as a metal scavenger. The resulting heterogeneous mixture was filtered through Celite®, concentrated and analysed. This procedure was employed to prepare 1,2-diaryl-1*H*-imidazoles **2a**–**l** (Table 2, Entries 1–12).

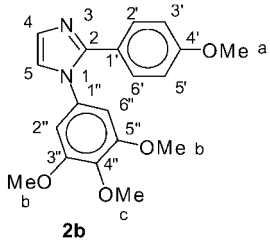
1,2-Diphenyl-1*H*-imidazole (2a): The crude reaction product obtained in Entry 1 of Table 2 from a Pd- and Cu-mediated reaction between **3a** and **4a** was purified by MPLC on silica gel with a mixture of AcOEt and toluene (50:50 + 0.1% Et_3N) as eluent and subsequent treatment with 3-(mercapto)propyl-functionalised silica gel to give **5a** (0.12 g, 55%) as a colourless solid: m.p. 77–79 °C (ref.[21] 80–81 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (m, 2 H, 3′-H and 5′-H), 7.43 (m, 3 H, 3′′-H, 5′′-H and 4′′-H), 7.33 (d, J

= 1.3 Hz, 1 H, 4-H), 7.30 (m, 1 H, 4′-H), 7.27 (m, 2 H, 2′-H and 6′-H), 7.24 (m, 2 H, 2′′-H and 6′′-H), 7.19 (d, *J* = 1.3 Hz, 1 H, 5-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 146.3 (C-2), 138.0 (C-1′′), 129.7 (C-3′′ and C-5′′), 129.5 (C-1′), 129.1 (C-4′), 128.8 (C-3′ and C-5′), 128.6 (C-4′′), 128.4 (C-2′ and C-6′), 127.5 (C-4′), 125.9 (C-2′′ and C-6′′), 122.9 (C-5) ppm. IR (KBr disk): $\tilde{\nu}$ = 1596, 1497, 1416, 1303, 1136, 1065, 744 cm^{-1}. EI-MS: *m*/*z* 221 (14) [*M* + 1]$^+$, 220 (90) [*M*]$^+$, 219 (100), 193 (12), 165 (6), 90 (11), 77 (18). The NMR spectroscopic data of this compound were in satisfactory agreement with those previously reported.[15c]



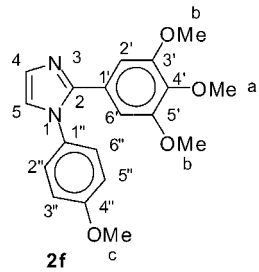
2a

2-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (2b): The crude reaction product obtained in Entry 11 of Table 2 from a Pd- and Cu-mediated reaction between **3b** and **4b** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (96:4) as eluent and subsequent treatment with 3-(mercapto)propyl-functionalised silica gel to give **2b** (0.18 g, 52%) as a light brown liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36 (m, 2 H, 2′-H and 6′-H), 7.20 (d, *J* = 1.2 Hz, 1 H, 4-H), 7.11 (d, *J* = 1.2 Hz, 1 H, 5-H), 6.79 (m, 2 H, 3′-H and 5′-H), 6.42 (s, 2 H, 2′′-H and 6′′-H), 3.87 (s, 3 H, OMe_c), 3.78 (s, 3 H, OMe_a), 3.72 (s, 6 H, OMe_b) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.7 (C-4′), 153.6 (C-3′′ and C-5′′), 146.5 (C-2), 137.8 (C-4′′), 134.2 (C-1′′), 129.8 (C-2′ and C-6′), 128.3 (C-4), 122.6 (C-1′), 122.4 (C-5), 113.6 (C-3′ and C-5′), 103.6 (C-2′′ and C-6′′), 61.0 (OMe_c), 56.2 (2×OMe_b), 55.2 (OMe_a) ppm. IR (neat): $\tilde{\nu}$ = 2939, 1609, 1597, 1506, 1254, 1127, 835 cm^{-1}. EI-MS: *m*/*z* (%) = 341 (21) [*M* + 1]$^+$, 340 (100) [*M*]$^+$, 325 (22), 298 (12), 282 (5), 255 (10), 147 (18). $C_{19}H_{20}N_2O_4$ (340.38): calcd. C 67.04, H 5.92; found: C 66.87, H 5.83.



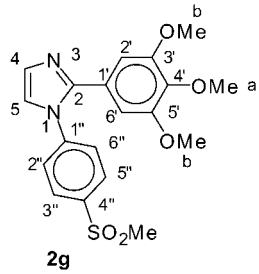
2b

1-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (2f): The crude reaction product obtained in Entry 3 of Table 2 from a Pd- and Cu-mediated reaction between **3c** and **4d** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (96:4) as eluent and subsequent treatment with 3-(mercapto)propyl-functionalised silica gel to give **2f** (0.20 g, 59%) as a light brown liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.30 (br. s, 1 H, 4-H), 7.21 (m, 2 H, 2′′-H and 6′′-H), 7.10 (br. s, 1 H, 5-H), 6.96 (m, 2 H, 3′′-H and 5′′-H), 6.69 (s, 2 H, 2′-H and 6′-H), 3.84 (s, 3 H, OMe_c), 3.83 (s, 3 H, OMe_a), 3.65 (s, 6 H, OMe_b) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.7 (C-4′′), 152.9 (C-3′ and C-5′), 146.2 (C-2), 138.6 (C-4′), 131.2 (C-1′′), 127.5 (C-2′′ and C-6′′), 127.3 (C-4), 124.2 (C-1′), 123.2 (C-5), 114.7 (C-3′′ and C-5′′), 105.9 (C-2′ and C-6′), 60.9 (OMe_a), 55.9 (2×OMe_b), 55.7 (OMe_c) ppm. IR (neat): $\tilde{\nu}$ = 2936, 1606, 1586, 1514, 1248, 1125, 838 cm^{-1}. EI-MS: *m*/*z* (%) = 341 (21) [*M* + 1]$^+$, 340 (100) [*M*]$^+$, 339 (28), 309 (10), 295 (5), 267 (7), 211 (4). $C_{19}H_{20}N_2O_4$ (340.38): calcd. C 67.02, H 5.92; found: C 66.84, H 5.80.



2f

1-[(4-Methylsulfonyl)phenyl]-2-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (2g): The crude reaction product obtained in Entry 4 of Table 2 from a Pd- and Cu-mediated reaction between **3d** and **4d** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent and subsequent treatment with 3-(mercapto)propyl-functionalised silica gel to give **2g** (0.31 g, 79%) as a light brown solid: m.p. 68–70 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.02 (m, 2 H, 3′′-H and 5′′-H), 7.47 (m, 2 H, 2′′-H and 6′′-H), 7.31 (s, 1 H, 4-H), 7.20 (s, 1 H, 5-H), 6.57 (s, 2 H, 2′-H and 6′-H), 3.84 (s, 3 H, OMe_a), 3.64 (s, 6 H, OMe_b), 3.08 (s, 3 H, SO_2Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.2 (C-3′ and C-5′), 146.7 (C-2), 142.9 (C-1′′), 140.4 (C-4′′), 139.1 (C-4′), 129.1 (C-4), 129.0 (C-3′′ and C-5′′), 126.7 (C-2′′ and C-6′′), 124.1 (C-1′), 122.5 (C-5), 61.0 (OMe_a), 56.0 (2×OMe_b), 44.0 (SO_2Me) ppm. IR (KBr disk): $\tilde{\nu}$ = 2902, 1588, 1497, 1459, 1421, 841 cm^{-1}. EI-MS: *m*/*z* (%) = 389 (23) [*M* + 1]$^+$, 388 (100) [*M*]$^+$, 387 (28), 374 (9), 373 (44), 180 (7), 179 (6). $C_{19}H_{20}N_2O_5S$ (388.45): calcd. C 58.75, H 5.19; found: C 59.07, H 5.03.

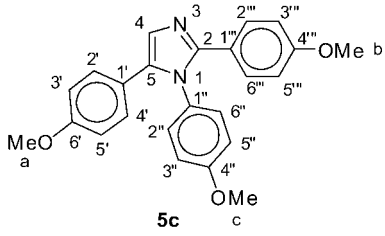


2g

The characterization of all the other 1,2-diaryl-1*H*-imidazoles prepared in this study can be found in the Supporting Information.

1,2,5-Tris(4-methoxyphenyl)-1*H*-imidazole (5c): 1-(4-Methoxyphenyl)-1*H*-imidazole (**3c**, 174 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (58 mg, 0.2 mmol), CuI (571 mg, 3.0 mmol), and CsF (456 mg, 3.0 mmol) were placed in a flame-dried reaction vessel, which was fitted with a silicon septum and evacuated and back-filled with argon in a sequence that was repeated twice. A solution of **4b** (702 mg, 3.0 mmol) in DMF (5 mL) was added by syringe at room temperature under a stream of argon. The resulting mixture was heated at 140 °C under argon with stirring and was maintained at this temperature for 281 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 compounds **5c**, **2c**, **4b** and 4,4′-(dimethoxy)biphenyl (**10a**). Since the degree of conversion of the reaction had not significantly increased after further stirring for 3 h, the reaction mixture was cooled to room temperature, diluted with AcOEt (50 mL) and poured

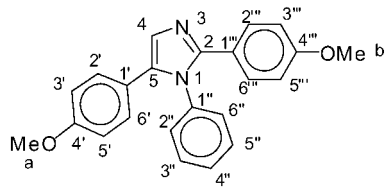
into a saturated aqueous NH_4Cl solution (30 mL). The resulting mixture was stirred in the open air for 0.5 h and extracted with AcOEt (4×35 mL). The organic extract was washed with brine (2×7 mL), dried and concentrated under reduced pressure, and the residue was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98:2) as eluent to give **5c** (139 mg, 36%) as a pale brown solid. This solid was then purified with 3-(mercapto) propyl-functionalised silica gel as a metal scavenger by the same procedure as had been used to purify compounds **2**. m.p. 56–58 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.46 (m, 2 H, 2‴-H and 6‴-H), 7.40 (s, 1 H, 4-H), 7.06 (m, 2 H, 2″-H and 6″-H), 7.02 (m, 2 H, 2′-H and 6′-H), 6.90 (m, 2 H, 3″-H and 5″-H), 6.85 (m, 2 H, 3‴-H and 5‴-H), 6.81 (m, 2 H, 3′-H and 5′-H), 3.89 (s, 3 H, OMe_b), 3.84 (s, 3 H, OMe_c), 3.78 (s, 3 H, OMe_a) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.8 (C-4‴), 160.6 (C-4″), 160.3 (C-4′), 145.0 (C-2), 135.5 (C-5), 131.2 (C-2‴ and C-6‴), 130.7 (C-2′ and C-6′), 129.2 (C-2″ and C-6″), 126.7 (C-1″), 118.7 (C-1′), 118.3 (C-4), 115.8 (C-1‴), 115.2 (C-3″ and C-5″), 114.6 (C-3‴ and C-5‴), 114.3 (C-3′ and C-5′), 55.6 (OMe_c), 55.5 (OMe_b), 55.3 (OMe_a) ppm. IR (KBr disk): $\tilde{\nu}$ = 1610, 1513, 1249, 1176, 1027, 833, 801 cm^{-1}. EI-MS: *m*/*z* (%) = 386 (100) $[M]^+$, 371 (26), 341 (5), 281 (9), 238 (4), 226 (5), 207 (15). $C_{24}H_{22}N_2O_3$ (386.45): calcd. C 74.59, H 5.74; found: C 74.82, H 5.81.



5c

2,5-Bis(4-methoxyphenyl)-1-phenyl-1*H*-imidazole (5e): This compound was synthesised by three different procedures (Methods A, B and C).

Method A: Compounds **3a** (144 mg, 1.0 mmol) and **4b** (468 mg, 2.0 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), CuI (381 mg, 2.0 mmol) and Cs_2CO_3 (652 mg, 2.0 mmol) were placed in a flame-dried reaction vessel, which was fitted with a silicon septum and then evacuated and back-filled with argon in a sequence that was repeated twice. DMF (5 mL) was then added by syringe at room temperature under a stream of argon and the resulting mixture was heated to 140 °C under argon with stirring and maintained at this temperature for 66 h. It was then cooled to room temperature, diluted with AcOEt (75 mL) and poured into a saturated aqueous NH_4Cl solution (35 mL). The resulting mixture was stirred in the open air for 0.5 h and extracted with AcOEt (4×60 mL). The organic extract was washed with brine (2×10 mL), dried and concentrated under reduced pressure. The residue was purified by MPLC on silica gel with a mixture of AcOEt and toluene (50:50 + 0.1% Et_3N) as eluent to give **5e** (114 mg, 32%) as a pale yellow solid: m.p. 176–178 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (m, 1 H, 4″-H), 7.38 (m, 2 H, 3″-H and 5″-H), 7.36 (br. s, 1 H, 4-H), 7.34 (d, *J* = 8.6 Hz, 2 H, 2‴-H and 6‴-H), 7.11 (m, 2 H, 2″-H and 6″-H), 6.99 (d, *J* = 8.4 Hz, 2 H, 2′-H and 6′-H), 6.79 (d, *J* = 8.6 Hz, 2 H, 3‴-H and 5‴-H), 6.76 (d, *J* = 8.4 Hz, 2 H, 3′-H and 5′-H), 3.78 (s, 3 H, OMe_b), 3.77 (s, 3 H, OMe_a) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.5 (C-4‴), 159.5 (C-4′), 144.6 (C-2), 136.2 (C-1″), 135.4 (C-5), 130.7 (C-4″), 130.6 (C-2‴ and C-6‴), 130.3 (C-3″ and C-5″), 130.2 (C-2′ and C-6′), 128.0 (C-2″ and C-6″), 123.6 (C-4), 120.8 (C-1′), 120.1 (C-1‴), 113.96 (C-3‴ and C-5‴), 113.95 (C-3′ and C-5′), 55.3 (OMe_b), 55.2 (OMe_a) ppm. IR (KBr disk): $\tilde{\nu}$ = 1608, 1498, 1250, 1174, 1030, 832, 772 cm^{-1}. EI-MS: *m*/*z* (%) = 357 (26) $[M + 1]^+$, 356 (100) $[M]^+$, 355 (25), 342 (8), 341 (30), 208 (6), 177 (10). $C_{23}H_{20}N_2O_2$ (356.42): calcd. C 77.51, H 5.66; found: C 77.39, H 5.57.



5e

Method B: 2-[(4-Methoxy)phenyl]-1-phenyl-1*H*-imidazole (**2e**, 146 mg, 0.58 mmol), $Pd(OAc)_2$ (6.5 mg, 2.9×10^{-4} mol), CuI (223 mg, 1.17 mmol) and CsF (178 mg, 1.17 mmol) were place in a flame-dried reaction vessel, which was fitted with a silicon septum and then evacuated and back-filled with argon in a sequence that was repeated twice. A solution of **4b** (274 mg, 1.17 mmol) in DMF (5 mL) was then added by syringe at room temperature under a stream of argon and the resulting mixture was stirred at 140 °C under argon and was maintained at this temperature for 113 h. It was then cooled to room temperature and worked up by the same procedure as used in Method A. A GLC analysis of the resulting crude reaction mixture showed that it contained compound **5e** in 57% GLC yield.

Method C: 5-[(4-Methoxy)phenyl]-1-phenyl-1*H*-imidazole (**1e**,[2] 146 mg, 0.58 mmol), $Pd(OAc)_2$ (6.5 mg, 2.9×10^{-4} mol), CuI (223 mg, 1.17 mmol) and CsF (178 mg, 1.17 mmol) were placed in a flame-dried reaction vessel, which was fitted with a silicon septum and then evacuated and back-filled with argon in a sequence that was repeated twice. A solution of **4b** (274 mg, 1.17 mmol) in DMF (5 mL) was then added by syringe at room temperature under a stream of argon and the resulting mixture was stirred at 140 °C under argon with stirring and maintained at this temperature for 46 h. The resulting yellow solution was then cooled to room temperature and worked up by the same procedure as used in Method A. A GLC analysis of the resulting crude reaction mixture showed that it contained compound **5e** in 74% GLC yield.

Supporting Information Available: Experimental procedures and characterization for compounds **2c**, **2d**, **2e**, **2h**, **2i**, **2j**, **2k** and **2l** and physical and spectroscopic data for compounds **5a** and **5d**. This material is available free of charge via the Internet (see footnote on the first page of this article).

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