Synthesis M. Lessi et al. Special Topic

Improved Synthesis of Symmetrical 2,5-Diarylimidazoles by One-Pot Palladium-Catalyzed Direct Arylation Tailored on the Electronic Features of the Aryl Halide

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Dedicated to Prof. Renzo Rossi on the occasion of his 80th birthday

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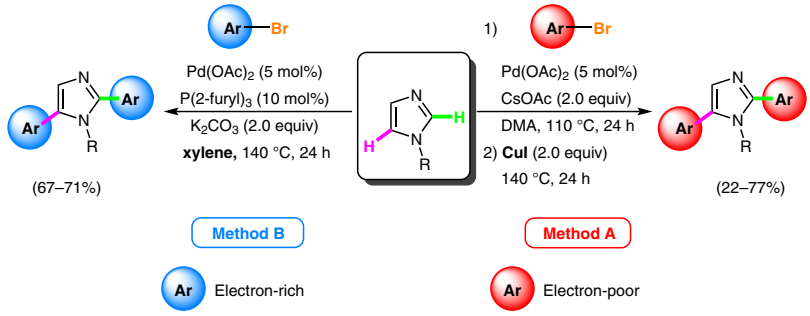
Abstract Two methods for the one-pot synthesis of 2,5-diarylimidazoles by palladium-catalyzed direct C–H arylation of 1-substituted imidazoles with aryl bromides have been devised. The first method, promoted by copper(I) iodide, is best suited for electron-poor aryl bromides, and also allows the 2,5-diarylation of thiazole and oxazole. The use of xylene instead of DMA is the key for the efficiency of the second method, which gives the best results with electron-rich aryl bromides.

Key words direct arylation, imidazoles, palladium, C–C coupling, regioselectivity, C–H bond activation, catalysis, aryl halides

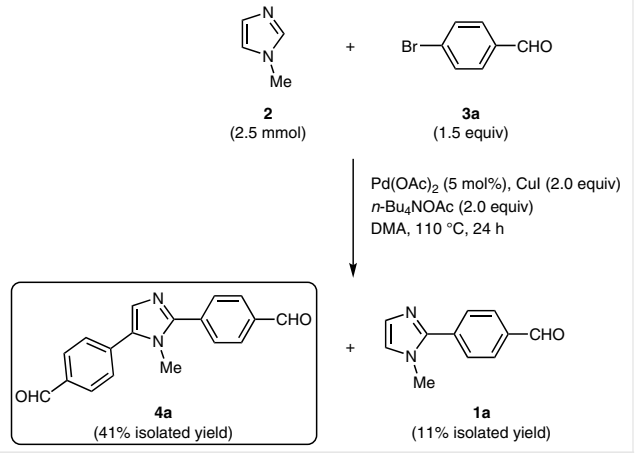


Aryl-substituted imidazoles represent a significant subclass of azoles found as the main structural core in several important families of compounds, including bioactive derivatives[1] and organic functional materials.[2] In this last field, imidazoles and, more generally, heteroaromatic compounds have emerged as privileged scaffolds for the development of organic fluorescent push–pull dyes.[2b,3] The presence of one or more heteroaromatic moieties in the skeleton of the fluorophore usually increases polarizability, due to the lower aromatic character when compared to benzene,[4] stability, and thermal and chemical robustness required for fabrication processes. Since the discovery in 1877 of the yellow chemiluminescence of lophine (2,4,5-triphenyl-1*H*-imidazole),[5] arylimidazoles have been used as synthetic scaffolds in charge-transfer fluorophores.[2b]

During our recent studies on the development of new imidazole-based organic fluorophores via palladium-catalyzed C–C bond-forming reactions,[6] we planned the preparation of 2-(4-formylphenyl)-1-methyl-1*H*-imidazole (**1a**) to be used as the electrophilic partner in Knoevenagel-type condensations.[6d] With this target in mind, 1-methyl-1*H*-imidazole (**2**) and 4-bromobenzaldehyde (**3a**) were reacted under the experimental conditions for the selective palladium/copper-mediated C-2 direct arylation promoted by *n*-Bu_4NOAc, previously developed by us.[7] However, in contrast to our expectations, the main product of this coupling was not **1a**, but a sparingly soluble yellow solid, which was subsequently identified as the symmetrical 2,5-diarylated imidazole **4a** (Scheme 1).

Imidazole **4a** showed interesting optical properties, displaying a very bright yellow-green fluorescence which is also retained in the solid state (Figure 1).

Intrigued by the fluorescence properties of this otherwise simple molecule, and after an extensive survey of the literature which provided no evidence of studies reporting the optical properties of this class of symmetrical push–pull fluorophores, we decided to focus our synthetic efforts



Scheme 1 First preparation of imidazole **4a**

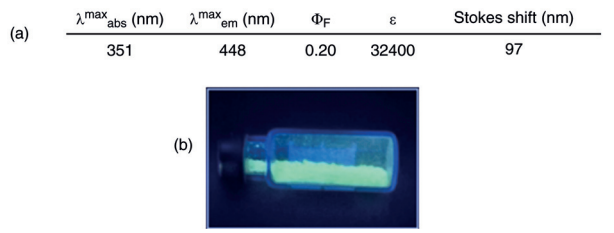


Figure 1 (a) Experimental spectroscopic data for imidazole **4a** as a 10^{-5} M THF solution. Fluorescence quantum yield was determined relative to quinine sulfate 0.1 M in H_2SO_4 ($\Phi = 0.54$), $\lambda_{exc} = 363$ nm. (b) Bright fluorescent powder of **4a** under a UV lamp at 366 nm.

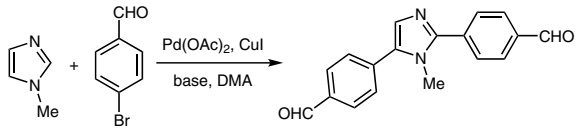
on the development of a viable procedure for the preparation of this class of compounds. In this paper, we summarize the results of our studies, which led us to develop two different one-pot direct C–H arylation protocols for the synthesis of 2,5-diarylated 1-substituted imidazoles **4**. The first protocol (Method A), best suited for electron-poor and electron-neutral bromides, consists of a two-step sequence involving at first the direct arylation of a 1-substituted imidazole with 3.0 equivalents of the appropriate aryl bromide in the presence of 5 mol% $Pd(OAc)_2$ and 2.0 equivalents of CsOAc in DMA at 110 °C for 24 hours, followed by the addition of 2.0 equivalents of CuI and a further 24 hours at 140 °C. On the contrary, the second protocol (Method B), a double arylation of a 1-substituted imidazole which requires 5 mol% $Pd(OAc)_2$ and 10 mol% P(2-furyl)$_3$ as the catalyst system in the presence of 3.0 equivalents of an aryl bromide and 2.0 equivalents of K_2CO_3 in xylene at 140 °C for 24 hours, fits better for electron-rich bromides.

The direct arylation reaction applied to the synthesis of aryl-substituted imidazoles represents one of the best procedures for obtaining this class of heteroaromatics.[8] However, despite several reported synthetic protocols for the regioselective palladium-catalyzed C-5[7,9] or C-2[7,9b,c,10] direct arylation of imidazoles, symmetrical 2,5-diaryl-substituted imidazoles **4** have been, in general, obtained in one-pot reactions only as unwanted byproducts during screenings devoted to establishing the best conditions for individual regioselective monoarylations[9b,d–g,10a,11] or aimed at the complete arylation of the imidazole nucleus.[12] In 2014, Doucet and co-workers reported the first intentional synthesis of several 2,5-diarylated 1-methylimidazoles **4** by a one-pot palladium-catalyzed direct arylation involving 1-methyl-1*H*-imidazole (**2**) and aryl bromides **3**.[13] These authors reported that the selection of the base appeared crucial for the reaction pattern, and the use of 4.0 equivalents of CsOAc in DMA along with a reaction temperature of 150 °C gave the best results in terms of chemical yield.

Taking into account that recent paper, we decided to start our survey by trying to replicate Doucet's results. Thus, we reacted 1-methyl-1*H*-imidazole (**2**) with 4-bromobenzaldehyde (**3a**) in the presence of 5 mol% $Pd(OAc)_2$ and 4.0 equivalents of CsOAc in DMA for 48 hours at 150 °C. In our hands, the coupling gave rise to the required **4a** too, but in a low 18% GLC yield, along with a large amount of the corresponding 5-monoarylated azole in a 40:60 GLC ratio with **4a**. Moreover, a byproduct, subsequently identified by GLC/MS analyses as likely an aldol-type condensation adduct between 4-bromobenzaldehyde (**3a**) and DMA, was also found in the reaction mixture.

Due to this unexpected negative result, we elected to set up a brief screening of the reaction conditions, starting from those of our serendipitous discovery depicted in Scheme 1. The results of this screening, which involved 1-methyl-1*H*-imidazole (**2**) and 4-bromobenzaldehyde (**3a**) as model reactants, are summarized in Table 1. In general, the data obtained confirm, on the one hand, that the presence of an inorganic base improves the yield and that, in agreement with Doucet and co-workers,[13] CsOAc is the best base among those examined. On the other hand, however, the results provide evidence that the presence of at least 2.0

Table 1 Screening of the Reaction Conditions for the Double Direct Arylation of 1-Methyl-1*H*-imidazole (**2**) with 4-Bromobenzaldehyde (**3a**)[a]



2 **3a** **4a**

Entry	Base	Time (h)	Temp (°C)	Yield of **4a** (%)[b]
1	*n*-Bu_4NOAc	24	110	46 (44)
2	K_2CO_3	24	110	50
3	Cs_2CO_3	24	110	56
4	KOAc	24	110	56
5	CsOAc	24	110	58 (55)
6[c]	CsOAc	24	110	32
7[d]	CsOAc	24	110	22
8[e]	CsOAc	24	110	46
9	CsOAc	24	90	28
10	CsOAc	24	140	64
11	CsOAc	48	110	59
12[f]	CsOAc	24 + 24	110 to 140	82 (77)

[a] Unless otherwise mentioned, reaction conditions: **2** (1.0 mmol), **3a** (3.0 equiv), $Pd(OAc)_2$ (5 mol%), CuI (2.0 equiv), base (2.0 equiv), DMA (5 mL), 110 °C, 24 h.
[b] GC yield. Isolated yield is given in parentheses.
[c] With CuI (1.0 equiv).
[d] With $Pd(OAc)_2$ (2 mol%).
[e] With P(*t*-Bu)$_3$ (10 mol%).
[f] This reaction was carried out for 24 h at 110 °C in the absence of CuI; then, CuI (2.0 equiv) was added, the temperature was raised to 140 °C, and the reaction mixture was stirred at this temperature for a further 24 h.

equivalents of CuI are mandatory to force the reaction towards the double C-5/C-2 arylation under ligandless conditions and using DMA as the solvent.

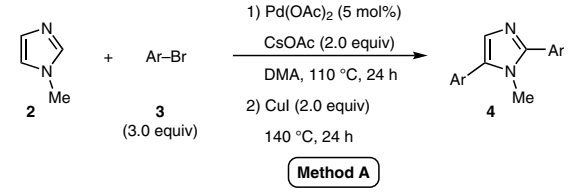
In detail, a fine tuning of the cationic and anionic moieties of the added base allowed an increase in the yield of **4a** (up to 55% isolated yield) when CsOAc was employed (Table 1, entry 5). In agreement with Doucet and co-workers,[13] better yields were obtained when cesium salts (Table 1, entries 3 and 5) were used instead of the corresponding potassium salts (Table 1, entries 2 and 4).

Regarding the anionic part of the base, acetates (Table 1, entries 4 and 5) resulted in a slightly higher efficiency than the corresponding carbonates (Table 1, entries 2 and 3). The use of *n*-Bu_4NOAc, which efficiently promotes the palladium-catalyzed C-5 direct arylation of oxazole, thiazole, and 1-methyl-1*H*-imidazole,[7] was in this case less effective than inorganic bases (Table 1, entry 1). A decreased loading of $Pd(OAc)_2$ or of CuI resulted in a serious decrease in the reaction yield (Table 1, entries 6 and 7). Finally, the use of 10 mol% P(*t*-Bu)$_3$, which has been reported to promote the 2,5-diarylation,[10a,12a] seems instead to have had a slight negative influence on the reaction yield when compared to the ligandless conditions (Table 1, entry 8).

Aiming to further improve the yield of **4a**, we examined the effect of temperature on the outcome of the coupling. While no formation of the desired product was observed after 24 hours at 70 °C, a progressive raising of the temperature from 90 °C to 110 °C increased the GLC yield of **4a** from 28% to 58% (Table 1, entries 9 and 5, respectively), while a further increment from 110 °C to 140 °C resulted in only a slight improvement to 64% yield (Table 1, entry 10). Given these results, we decided to test the potential benefit of increasing the reaction time from 24 to 48 hours (Table 1, entry 11); however, this last attempt left the reaction yield practically unaltered. Finally, we succeeded in enhancing the formation of **4a** by stirring the reaction mixture at 110 °C for 24 hours in the absence of CuI, then continuing for another 24 hours at 140 °C after the addition of 2.0 equivalents of CuI. With this last modification of the reaction procedure we were able to isolate **4a** in 77% yield (Table 1, entry 12).

This last improvement may be explained taking into account our previous results on the direct palladium- and copper-mediated arylation of 1,2- and 1,5-diarylimidazoles.[10a] In those studies, we found that the rate of the C-2 arylation of a typical 1,5-diaryl-1*H*-imidazole is higher than that of the C-5 arylation involving the corresponding 1,2-diaryl-1*H*-imidazole, and that the palladium- and copper-mediated direct C-2 arylation of 1-arylimidazoles is faster than the corresponding palladium-catalyzed direct C-5 arylation. Hence, when the reaction involving 1-methyl-1*H*-imidazole (**2**) is carried out in the presence of palladium and copper, the diarylated imidazole **4a** has to arise mainly from the C-5 arylation of the intermediate 2-aryl-1-methylimidazole, because the formation of that compound is faster than the formation of the 5-monoarylated regioisomer. But, as stated before, the C-5 arylation of a 2-arylated imidazole is slower than the C-2 arylation of a 5-arylated imidazole. As a consequence, starting from 1-methyl-1*H*-imidazole, we thought it appropriate to promote first the regioselective formation of the 5-monoarylated imidazole by working with palladium alone, and to subsequently add the copper salt to push the reaction to completion by C-2 arylation of the 5-arylated intermediate.[9g,10f]

Next, we evaluated the scope and the limitations of this one-pot palladium/copper-mediated double direct arylation by applying the reaction conditions of Table 1, entry 12 (Method A) to the preparation of several 2,5-diarylimidazoles **4** starting from 1-methyl-1*H*-imidazole (**2**) and (hetero)aryl bromides **3** (Scheme 2).

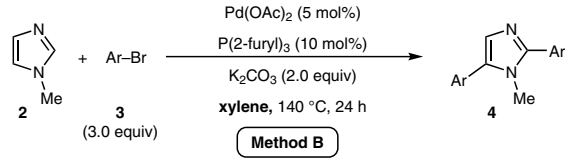


Scheme 2 Palladium- and copper-mediated one-pot synthesis of 2,5-diarylimidazoles **4** (Method A)

In detail, the direct arylation involving 4- or 3-substituted electron-poor aryl bromides **3a–j** proved to be clean and furnished the required imidazoles **4a–j** in 42–77% isolated yield (Table 2, entries 1–10). The reactions performed using Method A proved to be influenced by steric hindrance on the aryl bromide. In fact, 2-bromobenzonitrile (**3k**), a typical 2-substituted electron-poor aryl bromide, gave the corresponding 2,5-diarylated imidazole **4k** in only 30% isolated yield (Table 2, entry 11). Moreover, yields lower than 40% were obtained when two arbitrarily selected electron-poor heteroaryl bromides, 5-bromopyrimidine (**3q**) and 3-bromopyridine (**3r**), were used as the reaction partner (Table 2, entries 21 and 22).

Regarding electron-rich aryl bromides, the results using Method A were not completely satisfactory. The reaction of 4-bromotoluene (**3l**), 3-bromotoluene (**3m**), 2-bromotoluene (**3n**), and 4-bromoanisole (**3o**) gave the 2,5-diarylimidazoles **4l**, **4m**, **4n**, and **4o**, in 49%, 47%, 23%, and 33% isolated yield, respectively (Table 2, entries 12 and 14–16).

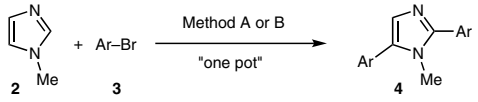
However, we found to our great delight that the use of xylene as solvent at 140 °C for 24 hours, in the presence of 2.0 equivalents of K_2CO_3 as the base and a combination of 5 mol% $Pd(OAc)_2$ and 10 mol% P(2-furyl)$_3$ as the catalyst system (Method B), allowed us to improve the efficiency of the one-pot double direct arylation when electron-rich bromides are used (Scheme 3).



Scheme 3 Palladium-catalyzed one-pot synthesis of electron-rich 2,5-diarylimidazoles **4** (Method B)

When Method B was applied, imidazoles **4l** and **4o** were actually isolated in 71% and 53% chemical yield (Table 2, entries 13 and 17).

Table 2 Synthesis of 2,5-Diaryl-1-methyl-1*H*-imidazoles **4** by One-Pot Double Direct Arylation of 1-Methyl-1*H*-imidazole (**2**) with Aryl Bromides **3**



Entry	3	Ar	Method[a]	4	Yield of 4 (%)[b]
1	**3a**	4-$OHCC_6H_4$	A	**4a**	77
2	**3b**	4-NCC_6H_4	A	**4b**	70
3	**3c**	4-$F_3CC_6H_4$	A	**4c**	51
4	**3d**	4-AcC_6H_4	A	**4d**	63
5	**3e**	4-$EtO_2CC_6H_4$	A	**4e**	59
6	**3f**	4-ClC_6H_4	A	**4f**	48
7	**3g**	4-$O_2NC_6H_4$	A	**4g**	37
8	**3h**	3-$F_3CC_6H_4$	A	**4h**	52
9	**3i**	3-$OHCC_6H_4$	A	**4i**	60
10	**3j**	3-FC_6H_4	A	**4j**	42
11	**3k**	2-NCC_6H_4	A	**4k**	30
12	**3l**	4-MeC_6H_4	A	**4l**	49
13	**3l**	4-MeC_6H_4	B	**4l**	71
14	**3m**	3-MeC_6H_4	A	**4m**	47
15	**3n**	2-MeC_6H_4	A	**4n**	23
16	**3o**	4-$MeOC_6H_4$	A	**4o**	33
17	**3o**	4-$MeOC_6H_4$	B	**4o**	53
18	**3p**	4-$Me_2NC_6H_4$	B	**4p**	67
19	**3a**	4-$OHCC_6H_4$	B	**4a**	27
20	**3g**	4-$O_2NC_6H_4$	B	**4g**	29
21	**3q**	5-pyrimidyl	A	**4q**	22
22	**3r**	3-pyridyl	A	**4r**	36

[a] Method A: 1) **2** (1.0 mmol), **3** (3.0 equiv), $Pd(OAc)_2$ (5 mol%), CsOAc (2.0 equiv), DMA (5 mL), 110 °C, 24 h; 2) CuI (2.0 equiv), 140 °C, 24 h. Method B: **2** (1.0 mmol), **3** (3.0 equiv), $Pd(OAc)_2$ (5 mol%), $P(2\text{-furyl})_3$ (10 mol%), K_2CO_3 (2.0 equiv), xylene (5 mL), 140 °C, 24 h.
[b] Isolated yield.

The reaction conditions of Method B arose from a screening of solvents and bases that was set up during our research, published in 2008, on the direct C-5 arylation of 1-methyl-1*H*-imidazole (**2**) with 4-bromoanisole (**3o**).[9h] In that screening, we found that when xylene was used as a solvent, instead of the more polar DMF or DMSO, at a reaction temperature of 140 °C, the coupling was particularly unselective, giving rise to a significant amount of the unrequired (at that time) 2,5-diarylimidazole **4o**. In the same study, we observed that an increase in the reaction temperature from 110 °C to 140 °C significantly favored the formation of **4o**. In fact, the GLC molar ratio between **4o** and the corresponding monosubstituted (at C-5 or C-2) imidazoles went from 1:99, when the reaction was carried out in toluene at 110 °C, to 87:13 when the same coupling was performed in xylene at 140 °C.[9h]

Disappointingly, when the reaction between 1-methyl-1*H*-imidazole (**2**) and 4-bromoanisole (**3o**) was carried out under Doucet's conditions[13] [i.e., CsOAc (4 equiv), $Pd(OAc)_2$ (5 mol%), DMA, 150 °C], we recorded an 11% GLC yield of the disubstituted imidazole **4o** vs an isolated yield of 78% reported by Doucet and co-workers. Even in this case, a significant amount of a monosubstituted imidazole was observed, very probably that arylated at C-5, in an 87:13 GLC ratio with the double 2,5-arylated imidazole **4o**.

Using the reaction conditions of Method B, we were also able to prepare 2,5-diarylimidazole **4p**, bearing the strong electron-donor dimethylamino group on both the C-2 and C-5 aromatic moieties. The preparation of **4p** was unsuccessful when Method A was tried for its synthesis (result not shown). Indeed, we proved that the two methods are complementary due to the fact that imidazoles **4a** and **4g**, bearing electron-poor aromatic moieties, were obtained in 27% and 29% isolated yield when Method B was applied (Table 2, entries 19 and 20), while the same compounds were isolated in 77% and 37% yield when Method A was used (Table 2, entries 1 and 7).

At present, we do not have sufficient data to fully explain the interesting role of xylene, which is particularly efficient but only when electron-rich aryl bromides are reacted with **2** as the electrophilic partner. However, the higher reactivity displayed by electron-rich bromides when compared with the electron-poor analogues points towards the possibility of a potential Pd(II)/Pd(IV) catalytic cycle,[14] instead of the well-established S_EAr or CMD (concerted metalation–deprotonation) mechanisms[15] which, on the contrary, both rely on Pd(0)/Pd(II) redox pathways. Our results are in fact similar, for example, to those very recently reported for the direct arylation of azoles in the presence of a pincer-ligated palladium complex.[16] In that study, the high reactivity observed when electron-rich aryl halides are the coupling partners was attributed to a better stabilization of Pd(IV) intermediates resulting from the oxidative addition of the aryl halide to a Pd(II) species.

Having obtained satisfactory results in the preparation of 1-methyl-1*H*-imidazoles **4** decorated at their positions 2 and 5 with electron-poor aryl groups via Method A, or bearing electron-rich aryl groups at the same positions via Method B, we decided to verify the feasibility of both methods for the synthesis of 2,5-diaryl-substituted azoles other than **4**. We were pleased to find that 1-phenyl-, 1-benzyl-, and 1-*n*-butyl-1*H*-imidazole (**5**, **6**, and **7**; Figure 2) are able to react with 3.0 equivalents of electron-poor aryl bromides **3** under the experimental conditions of Method A, giving rise to the required 2,5-diarylated 1-substituted imidazoles **8**, **9**, and **10** (Figure 2) in moderate to good yields (Table 3).

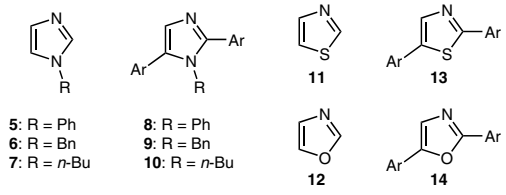
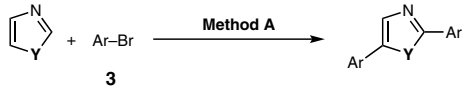


Figure 2 Chemical structures of azoles **5**, **6**, **7**, **11**, **12**, and of the corresponding 2,5-diarylated azoles **8**, **9**, **10**, **13**, **14**

Table 3 Synthesis of 2,5-Diaryl-Substituted Azoles by One-Pot Double Direct Arylation with Aryl Bromides **3**[a]



Entry	Product	Y	Ar	Yield (%)[b]
1	**8a**	N-Ph	4-OHCC$_6$H$_4$	38
2	**8b**	N-Ph	4-F$_3$CC$_6$H$_4$	44
3	**9a**	N-Bn	4-OHCC$_6$H$_4$	76
4	**9b**	N-Bn	4-F$_3$CC$_6$H$_4$	55
5	**9c**	N-Bn	4-ClC$_6$H$_4$	44
6	**9d**	N-Bn	4-NCC$_6$H$_4$	55
7	**10a**	N-*n*-Bu	4-NCC$_6$H$_4$	45
8	**10b**	N-*n*-Bu	4-ClC$_6$H$_4$	31
9	**13**	S	4-OHCC$_6$H$_4$	76
10	**14**	O	4-OHCC$_6$H$_4$	62

[a] Method A: 1) azole (1.0 mmol), **3** (3.0 equiv), Pd(OAc)$_2$ (5 mol%), CsOAc (2.0 equiv), DMA (5 mL), 110 °C, 24 h; 2) CuI (2.0 equiv), 140 °C, 24 h.
[b] Isolated yield.

In contrast, there was no formation of the expected 2,5-diarylated imidazoles, but significant amounts of the corresponding monoarylated derivatives were observed, when 1-phenyl-, 1-benzyl-, or 1-*n*-butyl-1*H*-imidazole (**5**, **6**, and **7**) was reacted with 3.0 equivalents of 4-bromoanisole (**3o**) or 4-bromotoluene (**3l**) under the reaction conditions of either Method A or Method B.

The experimental conditions of Method A also allowed the double C-2/C-5 arylation of thiazole (**11**) and oxazole (**12**). In fact, two typical 2,5-diaryl-substituted thiazole and oxazole compounds, **13** and **14** (Ar = 4-OHCC$_6$H$_4$), were isolated in 76% and 62% yield, respectively (Table 3, entries 9 and 10).

Concluding, in this study we developed two complementary methods for the efficient one-pot synthesis of 2,5-diarylimidazoles **4** by palladium-catalyzed direct arylation reactions. The first method requires a copper(I) salt as promoter, to force the C-2 arylation, under ligandless conditions. It gives good results when electron-poor aryl bromides are employed as the coupling partner. This protocol allows the 2,5-diarylation of 1-substituted imidazoles other than 1-methyl-1*H*-imidazole (**2**), and also of thiazole (**11**) and oxazole (**12**). The second method is copper-free, but employs tri(2-furyl)phosphine as palladium ligand and xylene as the solvent. This latter protocol works well with electron-rich aryl bromides, but was ineffective when imidazoles other than **2** were used, and gave unsatisfactory yields with electron-poor aryl bromides. The observed differences between the two methods can probably be attributed to diverse mechanistic pathways, namely CMD vs Pd(IV) intermediates.

The application of both methods to the efficient synthesis of new, thermally and photochemically stable, fluorescent push–pull fluorophores with large Stokes shifts and high fluorescence quantum yields is still in progress, and the results will be published in due course.

Melting points were recorded on a hot-stage microscope (Reichert Thermovar). Precoated silica gel PET foils (Sigma-Aldrich) were used for TLC analyses. GLC-FID analyses were performed on a Dani GC 1000 instrument equipped with a PTV injector and recorded with a Dani DDS 1000 data station. Three types of capillary columns were used: Agilent J&W HP-5ms column (30 m × 0.25 mm i.d. × 0.25 µm), Agilent J&W DB-5 column (30 m × 0.25 mm i.d. × 1 µm) and J&W DB-1 column (15 m × 0.25 mm i.d. × 0.25 µm). EIMS spectra were recorded at 70 eV by GLC/MS. GLC/MS analyses were performed on an Agilent 6890N gas chromatograph interfaced with an Agilent 5973N mass detector. ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer using TMS as an internal standard. ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer, operating at 100 MHz using the solvent signal as a reference. Standard abbreviations are used in reporting the NMR splitting patterns. Unless otherwise stated, all the reactions were performed under a positive atmosphere of argon by standard syringe, cannula, and septa techniques. 1-Methyl-1*H*-imidazole (**2**) was distilled under reduced pressure over CaH$_2$. CsOAc was stored in a desiccator. All the other reagents and solvents were purchased from Aldrich and used without further purification.

One-Pot Palladium/Copper-Mediated Synthesis of 2,5-Diarylimidazoles 4, 8, 9, 10, and of 2,5-Diarylthiazole 13 and 2,5-Diaryloxazole 14; General Procedure (Method A)

In a flame-dried reaction vessel were placed the appropriate aryl bromide **3** (3.0 mmol) and azole (1.0 mmol) if solid, Pd(OAc)$_2$ (11.2 mg, 0.050 mmol), and CsOAc (0.384 g, 2.00 mmol). The reaction vessel

was fitted with a silicon septum, evacuated, and back-filled with argon. This sequence was repeated twice. DMA (5 mL), the aryl bromide **3** (3.0 mmol) and the appropriate azole (1.0 mmol), if liquid, were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was stirred at 110 °C under argon for 24 h. CuI (0.380 g, 2.0 mmol) was then added to the resulting pale yellow mixture under a stream of argon. The reaction mixture was heated to 140 °C and stirred at this temperature for 24 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and poured into a saturated aqueous NH_4Cl solution. The resulting mixture was basified with a few drops of aqueous NH_4OH, stirred in the open air for 0.5 h, and then extracted with EtOAc. The organic extract was washed with water, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel or by crystallization. The chromatographic fractions containing the required compound were collected and concentrated. This procedure was employed to prepare 2,5-diaryl-1-methyl-1*H*-imidazoles **4a–o**,**q**,**r** (Table 2, entries 1–12, 14–16, 21, and 22), 2,5-diaryl-1-phenyl-1*H*-imidazoles **8a**,**b** (Table 3, entries 1 and 2), 2,5-diaryl-1-benzyl-1*H*-imidazoles **9a–d** (Table 3, entries 3–6), 2,5-diaryl-1-*n*-butyl-1*H*-imidazoles **10a**,**b** (Table 3, entries 7 and 8), 4,4′-(thiazole-2,5-diyl)dibenzaldehyde (**13**) (Table 3, entry 9), and 4,4′-(oxazole-2,5-diyl)dibenzaldehyde (**14**) (Table 3, entry 10).

One-Pot Palladium-Catalyzed Synthesis of 2,5-Diarylimidazoles 4 in Xylene; General Procedure (Method B)

In a flame-dried reaction vessel were placed the appropriate aryl bromide **3** (3.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), P(2-furyl)$_3$ (23.2 mg, 0.1 mmol), and K_2CO_3 (0.276 g, 2.0 mmol). The reaction vessel was fitted with a silicon septum, evacuated, and back-filled with argon. This sequence was repeated twice. Xylene (5 mL) and 1-methyl-1*H*-imidazole (**2**; 80.0 µL, 82.1 mg, 1.0 mmol) 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 24 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc/CH_2Cl_2 (1:1, 20 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel. The chromatographic fractions containing the required compound were collected and concentrated. This procedure was employed to prepare 2,5-diaryl-1-methyl-1*H*-imidazoles **4a**, **4g**, **4l**, **4o**, and **4p** (Table 2, entries 19, 20, 13, 17, and 18, respectively).

4,4′-(1-Methyl-1*H*-imidazole-2,5-diyl)dibenzaldehyde (4a)

The crude reaction product obtained from imidazole **2** and aryl bromide **3a** according to Method A was purified by flash chromatography on silica gel (EtOAc) (R_f = 0.34) to give **4a** (0.226 g, 77%) as a bright yellow solid. GLC analysis showed that **4a** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 164–165 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.12 (s, 1 H), 10.10 (s, 1 H), 8.05 (m, 2 H), 8.03 (m, 2 H), 7.94 (m, 2 H), 7.68 (m, 2 H), 7.28 (s, 1 H), 3.85 (s, 3 H).

EIMS: *m*/*z* (%) = 290 (100) [M$^+$], 289 (66), 158 (11), 130 (8), 103 (7), 89 (7).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.75; H, 4.87; N, 9.68.

4,4′-(1-Methyl-1*H*-imidazole-2,5-diyl)dibenzonitrile (4b)

The crude reaction product obtained from **2** and aryl bromide **3b** according to Method A was purified by crystallization (toluene) to give **4b** (0.200 g, 70%) as a yellow solid. GLC analysis showed that **4b** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 208–210 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (m, 6 H), 7.65 (m, 2 H), 7.42 (s, 1 H), 3.82 (s, 3 H).

EIMS: *m*/*z* (%) = 285 (21), 284 (100) [M$^+$], 283 (89), 207 (10), 155 (18), 128 (13).

Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.04; H, 4.25; N, 19.71. Found: C, 76.34; H, 4.26; N, 19.70.

1-Methyl-2,5-bis(4-(trifluoromethyl)phenyl)-1*H*-imidazole (4c)

The crude reaction product obtained from **2** and aryl bromide **3c** according to Method A was purified by crystallization (hexane) to give **4c** (0.189 g, 51%) as a yellow solid. GLC analysis showed that **4c** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[12a]

Mp 156–158 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (m, 2 H), 7.75 (m, 4 H), 7.59 (m, 2 H), 7.32 (s, 1 H), 3.73 (s, 3 H).

EIMS: *m*/*z* (%) = 370 (100) [M$^+$], 369 (82), 351 (12), 198 (13), 171 (7).

Anal. Calcd for $C_{18}H_{12}F_6N_2$: C, 58.38; H, 3.27; N, 7.57. Found: C, 58.60; H, 3.28; N, 7.59.

1,1′-((1-Methyl-1*H*-imidazole-2,5-diyl)bis(4,1-phenylene))bis(ethan-1-one) (4d)

The crude reaction product obtained from **2** and aryl bromide **3d** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 90:10) (R_f = 0.35) to give **4d** (0.201 g, 63%) as a pale yellow solid. GLC analysis showed that **4d** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 212–214 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (m, 4 H), 7.84 (m, 2 H), 7.58 (m, 2 H), 7.35 (s, 1 H), 3.77 (s, 3 H), 2.65 (s, 6 H).

EIMS: *m*/*z* (%) = 319 (22), 318 (100) [M$^+$], 317 (33), 303 (49), 275 (13).

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.74; H, 5.71; N, 8.77.

Diethyl 4,4′-(1-Methyl-1*H*-imidazole-2,5-diyl)dibenzoate (4e)

The crude reaction product obtained from **2** and aryl bromide **3e** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 30:70) (R_f = 0.35) to give **4e** (0.223 g, 59%) as a white solid. GLC analysis showed that **4e** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 168–170 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (m, 4 H), 7.81 (m, 2 H), 7.55 (m, 2 H), 7.33 (s, 1 H), 4.42 (q, *J* = 6.9 Hz, 4 H), 3.75 (s, 3 H), 1.43 (t, *J* = 6.9 Hz, 6 H).

EIMS: *m*/*z* (%) = 379 (25), 378 (100) [M$^+$], 377 (21), 349 (11), 321 (10).

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 70.09; H, 5.88; N, 7.38.

2,5-Bis(4-chlorophenyl)-1-methyl-1*H*-imidazole (4f)

The crude reaction product obtained from **2** and aryl bromide **3f** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 30:70) (R_f = 0.37) to give **4f** (0.146 g, 48%) as a pale brown solid. GLC analysis showed that **4f** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 154–155 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (m, 2 H), 7.41 (m, 6 H), 7.19 (s, 1 H), 3.64 (s, 3 H).

EIMS: *m*/*z* (%) = 306 (11), 305 (18), 304 (65), 303 (59), 302 (100) [M$^+$], 164 (19).

Anal. Calcd for $C_{16}H_{12}Cl_2N_2$: C, 63.38; H, 3.99; N, 9.24. Found: C, 63.61; H, 4.00; N, 9.25.

1-Methyl-2,5-bis(4-nitrophenyl)-1*H*-imidazole (4g)

The crude reaction product obtained from **2** and aryl bromide **3g** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 40:60) (R_f = 0.38) to give **4g** (0.120 g, 37%) as a pale orange solid. GLC analysis showed that **4g** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 218–220 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.43 (m, 4 H), 8.13–8.11 (m, 2 H), 7.93 (m, 2 H), 7.60 (s, 1 H), 3.88 (s, 3 H).

EIMS: *m*/*z* (%) = 325 (20), 324 (100) [M$^+$], 323 (32), 294 (28), 232 (16), 89 (11).

Anal. Calcd for $C_{16}H_{12}N_4O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.40; H, 3.74; N, 17.34.

1-Methyl-2,5-bis(3-(trifluoromethyl)phenyl)-1*H*-imidazole (4h)

The crude reaction product obtained from **2** and aryl bromide **3h** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 40:60) (R_f = 0.37) to give **4h** (0.193 g, 52%) as a pale yellow solid. GLC analysis showed that **4h** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 156–158 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.66 (m, 6 H), 7.29 (s, 1 H), 3.72 (s, 3 H).

EIMS: *m*/*z* (%) = 371 (20), 370 (100) [M$^+$], 369 (80), 351 (12), 198 (13).

Anal. Calcd for $C_{18}H_{12}F_6N_2$: C, 58.38; H, 3.57; N, 7.57. Found: C, 58.15; H, 3.58; N, 7.60.

3,3′-(1-Methyl-1*H*-imidazole-2,5-diyl)dibenzaldehyde (4i)

The crude reaction product obtained from **2** and aryl bromide **3i** according to Method A was purified by flash chromatography on silica gel (EtOAc) (R_f = 0.40) to give **4i** (0.174 g, 60%) as a pale orange solid. GLC analysis showed that **4i** had chemical purity higher than 98%.

Mp 108–110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.16 (s, 1 H), 10.05 (s, 1 H), 8.23 (s, 1 H), 7.97 (m, 4 H), 7.72 (m, 3 H), 7.32 (s, 1 H), 3.77 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.8, 191.7, 148.6, 137.0, 136.7, 134.7, 134.5, 134.3, 131.7, 131.1, 129.9, 129.8 (2 C), 129.6, 129.5, 129.2, 128.7, 34.0.

EIMS: *m*/*z* (%) = 291 (19), 290 (100) [M$^+$], 289 (57), 261 (8), 158 (9).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.76; H, 4.87; N, 9.68.

2,5-Bis(3-fluorophenyl)-1-methyl-1*H*-imidazole (4j)

The crude reaction product obtained from **2** and aryl bromide **3j** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 30:70) (R_f = 0.33) to give **4j** (0.114 g, 42%) as a pale brown solid. GLC analysis showed that **4j** had chemical purity higher than 98%.

Mp 117–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (m, 4 H), 7.17 (m, 5 H), 3.69 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8 (d, *J* = 246 Hz), 162.7 (d, *J* = 246 Hz), 148.5 (d, *J* = 2.4 Hz), 134.6 (d, *J* = 2.1 Hz), 132.7 (d, *J* = 8.2 Hz), 132.1 (d, *J* = 8.3 Hz), 130.5 (d, *J* = 8.5 Hz), 130.3 (d, *J* = 8.3 Hz), 128.3, 124.4 (d, *J* = 2.9 Hz), 124.3 (d, *J* = 2.9 Hz), 115.8 (d, *J* = 22.1 Hz, 2 C), 115.4 (d, *J* = 22.3 Hz), 114.9 (d, *J* = 21.0 Hz), 33.8.

EIMS: *m*/*z* (%) = 271 (17), 270 (100) [M$^+$], 269 (79), 148 (24), 107 (10).

Anal. Calcd for $C_{16}H_{12}F_2N_2$: C, 71.10; H, 4.48; N, 10.36. Found: C, 71.37; H, 4.49; N, 10.40.

2,2′-(1-Methyl-1*H*-imidazole-2,5-diyl)dibenzonitrile (4k)

The crude reaction product obtained from **2** and aryl bromide **3k** according to Method A was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 99:1) (R_f = 0.31) to give **4k** (0.085 g, 30%) as a pale brown solid. GLC analysis showed that **4k** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 190–192 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (m, 2 H), 7.73 (m, 3 H), 7.55 (m, 3 H), 7.44 (s, 1 H), 3.60 (s, 3 H).

EIMS: *m*/*z* (%) = 285 (19), 284 (100) [M$^+$], 283 (88), 258 (11), 155 (10), 114 (10).

Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.04; H, 4.25; N, 19.71. Found: C, 76.35; H, 4.26; N, 19.78.

1-Methyl-2,5-di-*p*-tolyl-1*H*-imidazole (4l)

The crude reaction product obtained from **2** and aryl bromide **3l** according to Method B was purified by flash chromatography on silica gel (EtOAc/toluene, 40:60) (R_f = 0.35) to give **4l** (0.186 g, 71%) as a pale yellow solid. GLC analysis showed that **4l** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 163–165 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (m, 2 H), 7.34 (m, 2 H), 7.26 (m, 4 H), 7.16 (s, 1 H), 3.64 (s, 3 H), 2.40 (s, 6 H).

EIMS: *m*/*z* (%) = 263 (20), 262 (100) [M$^+$], 261 (68), 144 (14), 117 (7).

Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.21; H, 6.94; N, 10.65.

1-Methyl-2,5-di-*m*-tolyl-1*H*-imidazole (4m)

The crude reaction product obtained from **2** and aryl bromide **3m** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 30:70) (R_f = 0.32) to give **4m** (0.123 g, 47%) as a pale yellow solid. GLC analysis showed that **4m** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 80–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 9 H), 3.66 (s, 3 H), 2.41 (s, 6 H).

EIMS: *m*/*z* (%) = 263 (19), 262 (100) [M$^+$], 261 (79), 144 (14), 117 (7).

Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.73; H, 6.93; N, 10.71.

1-Methyl-2,5-di-*o*-tolyl-1*H*-imidazole (4n)

The crude reaction product obtained from **2** and aryl bromide **3n** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 40:60) (R_f = 0.37) to give **4n** (0.060 g, 23%) as a pale yellow solid. GLC analysis showed that **4n** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 56–58 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 8 H), 7.08 (s, 1 H), 3.18 (s, 3 H), 2.28 (s, 3 H), 2.25 (s, 3 H).

EIMS: *m*/*z* (%) = 263 (18), 262 (100) [M$^+$], 261 (96), 248 (14), 247 (69), 144 (27), 130 (26).

Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.73; H, 6.94; N, 10.72.

2,5-Bis(4-methoxyphenyl)-1-methyl-1*H*-imidazole (4o)

The crude reaction product obtained from **2** and aryl bromide **3o** according to Method B was purified by flash chromatography on silica gel (EtOAc/toluene, 80:20) (R_f = 0.36) to give **4o** (0.156 g, 53%) as a pale yellow solid. GLC analysis showed that **4o** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[9h]

Mp 218–220 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (m, 2 H), 7.42 (m, 2 H), 7.22 (s, 1 H), 6.89 (m, 4 H), 3.72 (s, 3 H), 3.09 (s, 3 H), 3.08 (s, 3 H).

EIMS: *m*/*z* (%) = 295 (20), 294 (100) [M$^+$], 293 (31), 279 (37), 147 (7).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.74; H, 6.18; N, 9.55.

4,4′-(1-Methyl-1*H*-imidazole-2,5-diyl)bis(*N*,*N*-dimethylaniline) (4p)

The crude reaction product obtained from **2** and aryl bromide **3p** according to Method B was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) (R_f = 0.41) to give **4p** (0.215 g, 67%) as a pale brown solid. GLC analysis showed that **4p** had chemical purity higher than 98%.

Mp 180–182 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (m, 2 H), 7.31 (m, 2 H), 7.10 (s, 1 H), 6.83–6.73 (m, 4 H), 3.61 (s, 3 H), 2.98–2.97 (m, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 149.8, 149.1, 135.0, 129.4 (4 C), 125.6, 118.8, 118.1, 112.2 (2 C), 111.8 (2 C), 40.2 (2 C), 40.1 (2 C), 33.5.

EIMS: *m*/*z* (%) = 321 (22), 320 (100) [M$^+$], 319 (33), 306 (13), 305 (23), 159 (14), 158 (11).

Anal. Calcd for $C_{20}H_{24}N_4$: C, 74.97; H, 7.55; N, 17.48. Found: C, 75.26; H, 7.58; N, 17.54.

5,5′-(1-Methyl-1*H*-imidazole-2,5-diyl)dipyrimidine (4q)

The crude reaction product obtained from **2** and aryl bromide **3q** according to Method A was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) (R_f = 0.40) to give **4q** (0.052 g, 22%) as a yellow solid. GLC analysis showed that **4q** had chemical purity higher than 98%.

Mp 200–202 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.31 (s, 1 H), 9.28 (s, 1 H), 9.13 (s, 2 H), 8.90 (s, 2 H), 7.43 (s, 1 H), 3.80 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6 + CD_3OD): δ = 158.6, 158.1, 156.7 (2 C), 156.41, 156.35 (2 C), 145.2, 130.2, 125.6, 124.9, 33.9.

EIMS: *m*/*z* (%) = 239 (15), 238 (100) [M$^+$], 237 (90), 211 (17), 210 (59), 184 (16), 183 (21).

Anal. Calcd for $C_{12}H_{10}N_6$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.73; H, 4.24; N, 35.40.

3,3′-(1-Methyl-1*H*-imidazole-2,5-diyl)dipyridine (4r)

The crude reaction product obtained from **2** and aryl bromide **3r** according to Method A was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 93:7) (R_f = 0.50) to give **4r** (0.085 g, 36%) as a pale yellow solid. GLC analysis showed that **4r** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 137–139 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.97 (s, 1 H), 8.76 (s, 1 H), 8.65 (m, 2 H), 8.06 (d, *J* = 8.1 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.44 (m, 2 H), 7.31 (s, 1 H), 3.73 (s, 3 H).

EIMS: *m*/*z* (%) = 237 (13), 236 (100) [M$^+$], 235 (100), 131 (20), 104 (9).

Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.44; H, 5.14; N, 23.79.

4,4′-(1-Phenyl-1*H*-imidazole-2,5-diyl)dibenzaldehyde (8a)

The crude reaction product obtained from **5** and aryl bromide **3a** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 50:50) (R_f = 0.33) to give **8a** (0.127 g, 38%) as a pale yellow solid. GLC analysis showed that **8a** had chemical purity higher than 98%.

Mp 240–241 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1 H), 9.95 (s, 1 H), 7.75 (m, 4 H), 7.48 (m, 6 H), 7.24 (m, 2 H), 7.17 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.7, 191.6, 147.8, 136.7, 135.9, 135.8, 135.4, 135.2, 134.9, 130.6, 130.2 (2 C), 129.9 (2 C), 129.6 (3 C), 129.2 (2 C), 128.5 (2 C), 128.2 (2 C).

EIMS: *m*/*z* (%) = 353 (24), 352 (100) [M$^+$], 351 (56), 165 (11), 77 (8).

Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.70; H, 4.59; N, 7.97.

1-Phenyl-2,5-bis(4-(trifluoromethyl)phenyl)-1*H*-imidazole (8b)

The crude reaction product obtained from **5** and aryl bromide **3c** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 20:80) (R_f = 0.40) to give **8b** (0.190 g, 44%) as a pale pink solid. GLC analysis showed that **8b** had chemical purity higher than 98%.

Mp 174–176 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (m, 10 H), 7.19 (m, 2 H), 7.14 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 136.6, 134.5, 133.8, 133.1, 130.3 (q, *J* = 32 Hz), 130.1 (2 C), 129.8, 129.5 (q, *J* = 31 Hz), 129.4, 129.0 (2 C), 128.4 (2 C), 128.2 (2 C), 125.5 (q, *J* = 3.8 Hz, 2 C), 125.2 (q, *J* = 3.8 Hz, 2 C), 124.1 (q, *J* = 269 Hz), 124.0 (q, *J* = 270 Hz).

EIMS: *m*/*z* (%) = 433 (24), 432 (100) [M$^+$], 431 (66), 261 (4), 165 (4).

Anal. Calcd for $C_{23}H_{14}F_6N_2$: C, 63.89; H, 3.26; N, 6.48. Found: C, 64.14; H, 3.27; N, 6.50.

4,4′-(1-Benzyl-1*H*-imidazole-2,5-diyl)dibenzaldehyde (9a)

The crude reaction product obtained from **6** and aryl bromide **3a** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 70:30) (R_f = 0.40) to give **9a** (0.278 g, 76%) as a pale orange solid. GLC analysis showed that **9a** had chemical purity higher than 98%.

Mp 124–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.94 (s, 1 H), 9.92 (s, 1 H), 7.79 (m, 6 H), 7.44 (m, 3 H), 7.21 (m, 3 H), 6.84 (m, 2 H), 5.35 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.4, 191.3, 149.1, 136.7, 136.0, 135.9, 135.5, 135.5, 134.9, 130.2, 129.9 (2 C), 129.8 (2 C), 129.0 (2 C), 129.0 (2 C), 128.8 (2 C), 127.8, 125.5 (2 C), 48.9.

EIMS: *m*/*z* (%) = 367 (14), 366 (50) [M$^+$], 207 (8), 92 (8), 91 (100).

Anal. Calcd for $C_{24}H_{18}N_2O_2$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.98; H, 4.96; N, 7.68.

1-Benzyl-2,5-bis(4-(trifluoromethyl)phenyl)-1*H*-imidazole (9b)

The crude reaction product obtained from **6** and aryl bromide **3c** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 20:80) (R_f = 0.38) to give **9b** (0.245 g, 55%) as a pale yellow solid. GLC analysis showed that **9b** had chemical purity higher than 98%.

Mp 107–109 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (m, 2 H), 7.62 (m, 4 H), 7.41 (m, 3 H), 7.28 (m, 3 H), 6.88 (m, 2 H), 5.29 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 137.1, 134.6, 134.1, 133.5, 131.0 (q, *J* = 33 Hz), 130.3 (q, *J* = 32 Hz), 129.7, 129.2 (2 C), 129.0 (4 C), 128.1, 125.8 (q, *J* = 3.7 Hz, 2 C), 125.73 (q, *J* = 3.7 Hz, 2 C), 125.67 (2 C), 124.02 (q, *J* = 272 Hz), 123.99 (q, *J* = 272 Hz), 48.9.

EIMS: *m*/*z* (%) = 447 (19), 446 (67) [M$^+$], 427 (10), 157 (10), 91 (100).

Anal. Calcd for $C_{24}H_{16}F_6N_2$: C, 64.58; H, 3.61; N, 6.28. Found: C, 64.83; H, 3.62; N, 6.30.

1-Benzyl-2,5-bis(4-chlorophenyl)-1*H*-imidazole (9c)

The crude reaction product obtained from **6** and aryl bromide **3f** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 20:80) (R_f = 0.44) to give **9c** (0.167 g, 44%) as a pale yellow solid. GLC analysis showed that **9c** had chemical purity higher than 98%.

Mp 166–168 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (m, 2 H), 7.28 (m, 10 H), 6.84 (m, 2 H), 5.22 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 137.3, 135.1, 134.3, 134.3, 130.2 (2 C), 130.0 (2 C), 129.3, 129.0 (2 C), 129.0 (2 C), 128.9 (2 C), 128.8, 128.5, 127.8, 125.7 (2 C), 48.6.

EIMS: *m*/*z* (%) = 380 (49), 379 (18) [M$^+$], 378 (74), 289 (25), 287 (38), 123 (24), 91 (100).

Anal. Calcd for $C_{22}H_{16}Cl_2N_2$: C, 69.67; H, 4.25; N, 7.39. Found: C, 69.94; H, 4.46; N, 7.41.

4,4′-(1-Benzyl-1*H*-imidazole-2,5-diyl)dibenzonitrile (9d)

The crude reaction product obtained from **6** and aryl bromide **3b** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 30:70) (R_f = 0.36) to give **9d** (0.198 g, 55%) as a pale yellow solid. GLC analysis showed that **9d** had chemical purity higher than 98%.

Mp 129–131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (m, 2 H), 7.63 (m, 4 H), 7.43 (m, 3 H), 7.30 (m, 3 H), 6.88 (s, 2 H), 5.33 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 136.6, 134.7, 134.5, 134.2, 132.6 (2 C), 132.5 (2 C), 130.5, 129.4 (2 C), 129.1 (2 C), 129.0 (2 C), 128.3, 125.5 (2 C), 118.41, 118.38, 112.7, 112.0, 49.1.

EIMS: *m*/*z* (%) = 361 (8), 360 (29) [M$^+$], 269 (2), 114 (9), 91 (100), 65 (7).

Anal. Calcd for $C_{24}H_{16}N_4$: C, 79.98; H, 4.47; N, 15.55. Found: C, 80.29; H, 4.47; N, 15.61.

4,4′-(1-Butyl-1*H*-imidazole-2,5-diyl)dibenzonitrile (10a)

The crude reaction product obtained from **7** and aryl bromide **3b** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 30:70) (R_f = 0.38) to give **10a** (0.147 g, 45%) as a pale brown solid. GLC analysis showed that **10a** had chemical purity higher than 98%.

Mp 141–142 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (m, 6 H), 7.60 (m, 2 H), 7.29 (s, 1 H), 4.18 (t, *J* = 7.4 Hz, 2 H), 1.31 (m, 2 H), 0.96 (m, 2 H), 0.64 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 135.2, 134.6, 133.7, 132.6 (2 C), 132.3 (2 C), 130.1, 129.2 (2 C), 128.8 (2 C), 118.3, 118.2, 112.3, 111.7, 45.2, 32.1, 19.0, 13.0.

EIMS: *m*/*z* (%) = 327 (25), 326 (100) [M$^+$], 283 (14), 271 (12), 270 (59), 114 (14).

Anal. Calcd for $C_{21}H_{18}N_4$: C, 77.28; H, 5.56; N, 17.17. Found: C, 77.58; H, 5.58; N, 17.20.

1-Butyl-2,5-bis(4-chlorophenyl)-1*H*-imidazole (10b)

The crude reaction product obtained from **7** and aryl bromide **3f** according to Method A was purified by flash chromatography on silica gel (EtOAc/toluene, 20:80) (R_f = 0.40) to give **10b** (0.107 g, 31%) as a pale brown solid. GLC analysis showed that **10b** had chemical purity higher than 98%. The NMR spectroscopic data of this compound were in agreement with those previously reported.[13]

Mp 125–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (m, 2 H), 7.45 (m, 4 H), 7.36 (m, 2 H), 7.13 (s, 1 H), 4.05 (t, *J* = 7.4 Hz, 2 H), 1.28 (m, 2 H), 0.95 (m, 2 H), 0.63 (t, *J* = 7.3 Hz, 3 H).

EIMS: *m*/*z* (%) = 346 (66), 345 (24), 344 (100) [M$^+$], 288 (42), 123 (19).

Anal. Calcd for $C_{19}H_{18}Cl_2N_2$: C, 66.09; H, 5.25; N, 8.11. Found: C, 66.34; H, 5.27; N, 8.14.

4,4′-(Thiazole-2,5-diyl)dibenzaldehyde (13)

The crude reaction product obtained from thiazole (**11**) and aryl bromide **3a** according to Method A was purified by crystallization (EtOAc) to give **13** (0.223 g, 76%) as an orange solid. GLC analysis showed that **13** had chemical purity higher than 98%.

Mp 155–157 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.08 (s, 1 H), 10.05 (s, 1 H), 8.23 (s, 1 H), 8.16 (m, 2 H), 7.98 (m, 4 H), 7.79 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.4, 191.2, 166.8, 141.5, 139.4, 138.3, 137.3, 136.8, 136.1, 130.7 (2 C), 130.5 (2 C), 127.1 (2 C), 127.0 (2 C).

EIMS: *m*/*z* (%) = 294 (22), 293 (100) [M$^+$], 292 (19), 162 (25), 161 (54).

Anal. Calcd for $C_{17}H_{11}NO_2S$: C, 69.61; H, 3.78; N, 4.77. Found: C, 69.87; H, 3.79; N, 4.78.

4,4′-(Oxazole-2,5-diyl)dibenzaldehyde (14)

The crude reaction product obtained from oxazole (**12**) and aryl bromide **3a** according to Method A was purified by crystallization (EtOAc) to give **14** (0.172 g, 62%) as an orange solid. GLC analysis showed that **14** had chemical purity higher than 98%.

Mp 194–196 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.09 (s, 1 H), 10.03 (s, 1 H), 8.29 (m, 2 H), 8.01 (m, 4 H), 7.91 (m, 2 H), 7.69 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.1, 191.9, 160.0, 150.4, 137.1, 135.7, 132.0, 130.9, 130.0 (2 C), 129.8 (2 C), 127.1, 126.5 (2 C), 124.4 (2 C).

EIMS: *m*/*z* (%) = 278 (18), 277 (100) [M$^+$], 276 (32), 165 (16), 89 (10).

Anal. Calcd for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.93; H, 3.99; N, 5.07.

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Supporting Information

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