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Direct Arylation of Simple Azoles Catalyzed by 1,10-Phenanthroline Containing Palladium Complexes: An Investigation of C4 Arylation of Azoles and the Synthesis of Triarylated Azoles by Sequential Arylation

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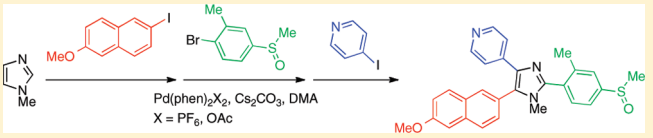
Supporting Information

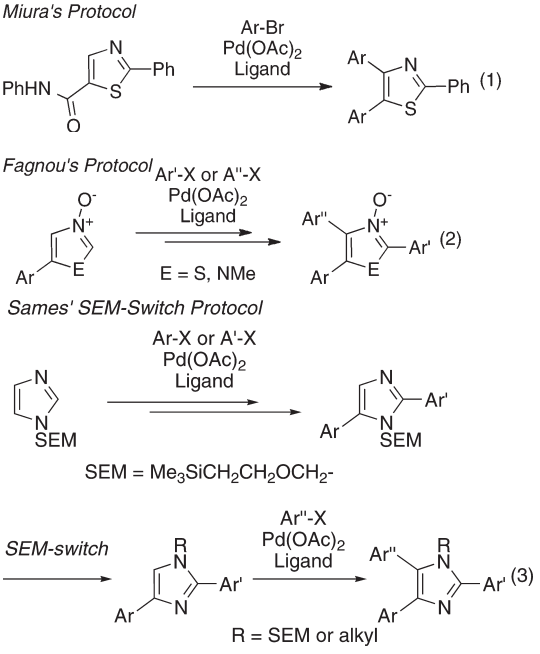
ABSTRACT: Direct triarylation and sequential triarylation reactions of simple azoles catalyzed by $[Pd(phen)_2]PF_6$ are described. Simple azoles, such as *N*-methylimidazole, thiazole, and oxazole, were observed to undergo triaryaltion reactions even at their C4 positions when treated with aryl iodides in the presence of $[Pd(phen)_2]PF_6$ as a catalyst and a stoichiometric amount of Cs_2CO_3 in DMA at 150 °C. Using excess amounts of azoles, selective C5 monoarylation was achieved by using the same catalytic system. Subsequent efforts demonstrated that C5 arylated azoles undergo exclusive C2 arylation using $[Pd(phen)_2]PF_6$ as the catalyst with galvinoxyl as an additive. Finally, unprecedented C4 arylation reactions of 2,5-diaryl-azoles occur by using the new catalytic system to give the corresponding triarylated products in good to excellent yields. The results of mechanistic studies suggest that the C2 arylation process takes place by way of an electrophilic aromatic substitution (S_EAr) palladation pathway, while arylation reactions at the C4 position occur via a S_EAr palladation and/or radical mechanism. Finally, a concise, three-step synthesis of the Tie-2 Tyrosine Kinase Inhibitor has been executed starting with commercially available *N*-methylimidazole by a route that employs the new sequential arylation process.



INTRODUCTION

Polyarylated azoles are important motifs in pharmaceuticals[1] and functional materials.[2] For example, triaryl-imidazoles, -oxazoles, and -thiazoles display valuable bioactivities that include kinase inhibition associated with antitumor activity.[3] Also, large numbers of materials used in organic electronic devices are composed of polyarylated heterocyclic structures.[2] Owing to the importance of their properties, polyarylated azoles have received great attention from the synthetic community. Historically, cyclization processes based on substitution and/or condensation reactions of carbonyl compounds and/or halides have been used to prepare substituted azoles.[4] However, these strategies often translate into elaborate multistep syntheses. In the past three decades, transition-metal-catalyzed cross-coupling reactions of (hetero)aryl halides and (hetero)aryl metal regents[5,6] have been developed for the preparation of substituted azoles even though electron-rich heteroaryl metal species, including heteroaryl−transition metal intermediates in these processes, are often unstable and readily undergo protonolysis or decomposition under the reaction conditions.[7]

The synthetic potential of transition-metal-catalyzed direct C−H bond arylation reactions of heteroarenes has recently attracted significant attention.[8−13] In fact, these processes do not require the use of preformed metal reagents, and as a result, a wide variety of five-membered heteroarenes can be utilized. In addition, a large effort has been directed at developing methods for executing multiple C−H arylations of simple azoles in order to produce polyarylated azoles.[14] In this regard, Miura has recently described a procedure for the synthesis of triarylated azoles that involves 4,5-diarylation of 2-aryl-azoles that contain a directing and sacrificial 5-carboxanilide group (eq 1).[14b,15] Fagnou also reported a method for preparation of triarylated azoles containing three different aryl groups that employs sequential C−H bond arylation of azole *N*-oxides (eq 2).[16]



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In light of these recent developments, studies of sequential arylation reactions that can be performed using simple and readily available azoles and that overcome problems associated with the low reactivity at C4 azole positions are worthwhile (Figure 1).[17] To circumvent the C4 reactivity issue, Sames has devised a SEM-switch strategy that employs an indirect method for introduction of a C4 aryl group in imidazole.[17] However, this protocol requires SEM protection and deprotection of nitrogen to achieve selective C4 arylation (eq 3). Recently, we reported that a palladium complex, bearing an sp^2-nitrogen-based ligand, such as 1,10-phenanthroline, displays excellent catalytic activity in C−H bond arylation reactions of simple azoles. Moreover, by using $[Pd(phen)_2](PF_6)_2$ (**1**) as a catalyst for these processes, all three sites including C4 in imidazole and oxazole are sequentially arylated in moderately efficient one-pot processes.[18] Furthermore, no additives, such as carboxylic acids,[16a] metal salts,[8l,n] and ammonium salts,[8r] are needed in these reactions except for a stoichiometric amount of a base to neutralize the formed hydrogen halides. It is important to note that prior to these findings, metal catalysts with nitrogen-based ligands have rarely been applied to direct C−H arylation reactions. Our studies with $[Pd(phen)_2](PF_6)_2$ have revealed that arylation reactions take place smoothly even at the C4 positions of simple 2,5-diaryl-azoles. Below, the full details of the investigation we have carried out in this area are described. The observations made in this effort demonstrate the significant synthetic potential of reactions promoted by the new catalytic system. This utility of this methodology is shown by its application to a concise three-step synthesis of the Tie-2 Tyrosine Kinase Inhibitor starting with commercially available *N*-methylimidazole.

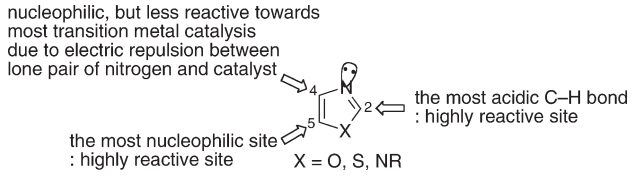
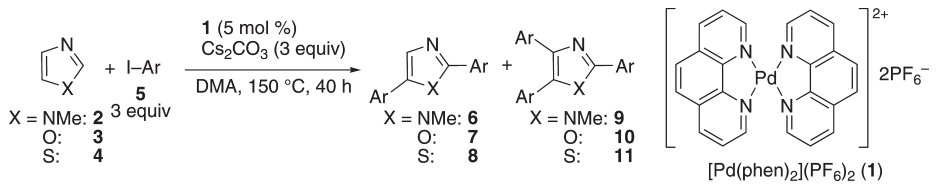


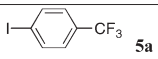
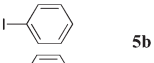
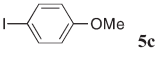
Figure 1. General reaction profiles for azoles in transition metal catalysis.

RESULTS AND DISCUSSIONS

One-Pot Multiple Direct C−H Arylation Reactions of Azoles with Aryl Halides Catalyzed by $[Pd(phen)_2](PF_6)_2$. The first phase of this investigation focused on an exploration of the scope of the triarylation reactions of azoles with aryl iodides promoted by $[Pd(phen)_2](PF_6)_2$ (**1**). Reactions of *N*-methylimidazole (**2**) with 3 equiv of the aryl iodides **5a**−**c** in DMA solutions containing catalyst **1** (5 mol %) and Cs_2CO_3 (3 equiv) gave the corresponding triarylated products **9** in good yields along with diarylated products **6** in 40−44% yields (Table 1, entries 1−3). Reactions of oxazole (**3**) with aryl iodides under these conditions also gave the triarylated products **10** in moderate to high yields (entries 4−6). In addition, the triaryalted product **10** was obtained in quantitative yield when 10 mol % of catalyst **1** was used (entry 4). In contrast, triarylated products **11** were not produced when thiazole (**4**) and aryl iodides were subjected to the palladium-catalyzed reaction conditions. Instead, diarylated products **8** were generated exclusively in 73−99% yields (entries 7−9). The finding that *N*-methylimidazole and oxazole undergo triarylation reactions demonstrates that by using the $[Pd(phen)_2](PF_6)_2$ catalyst C4 arylation of 1,3-azoles takes place. In addition, the triarylation process can be applied to the other types of azoles, exemplified by transformation of

Table 1. One-Pot Direct Multiple Arylation Reactions of Azoles Catalyzed by $[Pd(phen)_2](PF_6)_2$[a]



entry	azoles	5	product (isolated yield) di	product (isolated yield) tri
1	 2	 5a	**6a**(39%)	**9a**(59%)
2		 5b	**6b**(31%)	**9b**(61%)
3		 5c	**6c**(40%)	**9c**(44%)
4	 3	5a	**7a**(21%)(3%)[b]	**10a**(76%)(96%)[b]
5		5b	**7b**(34%)	**10b**(55%)
6		5c	**7c**(30%)	**10c**(49%)
7	 4	5a	**8a**(73%)[c]	**11a**(trace)
8		5b	**8b**(93%)[c]	**11b**(trace)
9		5c	**8c**(99%)[c]	**11c**(trace)

[a] The reactions were carried out with 0.5 mmol of azoles **2**−**4**. [b] The isolated yield of the reaction with 10 mol % of **1**. [c] The reaction was carried out with 6 equiv of aryl iodide for 20 h.

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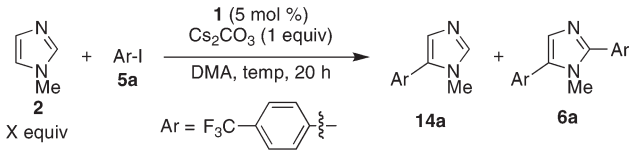
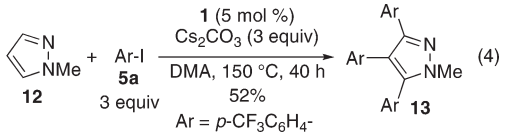
Table 2. Optimization of C5 Direct Monoarylation of *N*-Methylimidazole Catalyzed by $[Pd(phen)_2](PF_6)_2$[a]



			yield (%)[b]	
entry	equiv of **2**	temp (°C)	**14a**	**6a**
1	1.1	150	trace	93
2	1.1	140	46	54
3	1.1	130	40	36
4	2	150	33	58
5	3	150	59	40
6	10	150	74	trace

[a] The reactions were carried out with 0.5 mmol of *p*-$CF_3C_6H_4$-I. [b] Isolated yields based on the amount of *p*-$CF_3C_6H_4$-I.

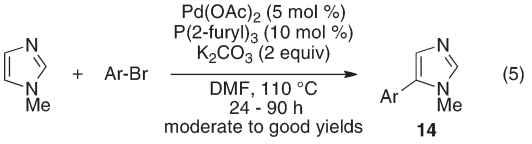
N-methylpyrazole (**12**) to the tris-*p*-trifluoromethylphenyl adduct **13** in a moderate yield (eq 4).



Sequential Direct C−H Arylation of *N*-Methylimidazole. In order to explore further the unprecedented reactions promoted by the catalytic system described above, stepwise sequential arylation reactions of azoles that enable introduction of three different aryl groups into the azole skeleton were investigated. Inspection of the observations made in earlier efforts suggests that the positional reactivity profile of azoles, in particular imidazole, in palladium-catalyzed C−H bond arylation processes is either C5 ≥ C2 ≫ C4 or C2 ≥ C5 ≫ C4 depending on the catalytic system employed.[8j,l] As a result, selective arylation at C5 or C2 can be achieved by using the reported catalytic systems. Nevertheless, undesired secondary reactions of the initially formed C5 and C2 arylated products that lead to diarylation and the low efficiencies of arylation reactions of monoarylated substrates are issues that need to be solved in order to promote efficient sequential arylation processes. Therefore, further investigations of the reaction conditions for arylation on each three positions of *N*-methylimidazole were carried out.

Site-Selective C5-Arylation Reactions of *N*-Methylimidazole Catalyzed by $[Pd(phen)_2](PF_6)_2$. A number of C5 arylation reactions of azoles have been described previously.[14b,15,18,19] In the reported processes, C5-aryl-azoles often display a higher reactivity at C2 positions compared to those of unsubstituted azoles. Thus C5,C2 diarylation of azoles often serves as a yield diminishing side reaction in processes designed to form mono-C5 arylated products. In this context, Bellina and Rossi developed a selective C5 arylation reaction that employs $Pd(OAc)_2$/$P(2\text{-furyl})_3$/K_2CO_3 as the catalytic system (eq 5).[19] Although this process is relatively slow, it does furnish the C5-arylated imidazoles **14** selectively and in good yield.

To investigate the applicability of $[Pd(phen)_2](PF_6)_2$ to monoarylation reactions, we have examined reactions of *N*-methylimidazole (**2**) under controlled conditions. The results, displayed in Table 2, show that reaction of **2** with a nearly stoichiometric amount of aryl iodide **5a** at 150 °C for 20 h gave the diaryl-imidazole **6a** in quantitative yield based on **5a** (entry 1). Reaction under the same conditions carried out at the 140 °C led to formation of the monoarylated product **14a** in 46% yield, but the diarylated product **6a** is still formed in 54% yield. Although lowering the temperature further (130 °C) enables **14a** to be produced in higher yield than **6a**, the total yield of **14a** and **6a** at this temperature is lower (entry 3). The quantity of *N*-methylimidazole (**2**) has an impact on ratio of monoarylated **14a** and diarylated **6a** products. Specifically, the selectivity for formation of **14a** was increased when increasing amounts of **2** were employed (entries 4−6), and the use of 10 equiv of **2** resulted in exclusive generation of the monoarylation product (entry 6). Owing to ready availability of **2**, reactions of 10 equiv of **2** with several aryl iodides were probed. As the results in Scheme 1 show, each of these reactions gave the corresponding monoarylated product **14** in high yield.



Site-Selective C2 Arylation of C5-Arylated *N*-Methylimidazoles. Selective C2 arylation reactions of C5-aryl-imidazoles **14** was investigated next. As the results previously shown in Table 2, the reactions of these substrates with aryl iodides employing catalyst **1** preferentially generated diarylated products. These observations clearly show that the new catalytic system is effective for conducting efficient C2 arylation reactions. Optimization of the conditions used for this process were carried out employing *N*-methyl-5-phenylimidazole (**14b**) and *p*-trifluoromethylphenyl iodide (**5a**). During the investigation, formation of the undesired triarylated product **16d** was an issue. The results displayed in Table 3 indicate that reactant concentration has an effect on the selectivity for production of the monoarylated product **15d** versus the triaryl-adduct **16d** (entries 1 and 2). The counteranion of the catalysts also governs the outcome of this process with the highest yield and selectivity for formation of **15d** being attained when the hexafluorophosphate containing catalyst **1** was used (entries 2−4). The optimum temperature for this reaction is 150 °C, since the use of both higher (160 °C) and lower (140 °C) temperatures led to lower yields of **15d** (entries 5 and 6). Thus, the reaction conditions listed in entry 2 were used in subsequent reactions. In addition, as part of mechanistic investigations described below, we observed that the triarylation reaction (further C4-arylation) is significantly suppressed when galvinoxyl is employed as an additive, as demonstrated by the formation of **15d** in 74% yield and no triarylated product (entry 7). This effect is likely the consequence of the operation of different mechanisms for the reactions occurring at different imidazole positions (see below).

An exploration of the substrate scope of the process provided the results summarized in Table 4. First, the electronic effects of substituents in both the aryl iodides **5** and the C5 aryl ring of imidazoles **14** on the reaction were examined (entries 1−9). The results indicate that the yields of products **6** and **15** are relatively higher when an electron-rich halide **5c** is used as the substrate (entries 2, 5, 8). In addition, the imidazole **14a**, which possesses an electron-withdrawing *p*-trifluoromethylphenyl group at C5,

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Scheme 1. Scope of the C5-Monoarylation Reaction of *N*-Methylimidazole

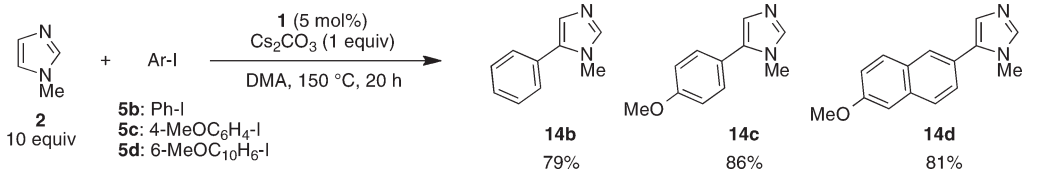
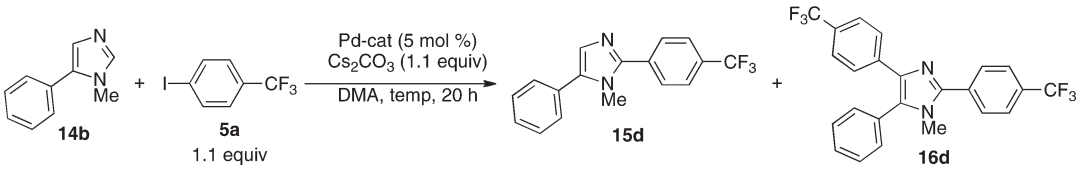


Table 3. Optimization of the Direct C2 Arylation of *N*-Methyl-5-phenylimidazole[a]



				yields (%)[b]	
entry	Pd cat.	concn (M)	temp (°C)	**15d**	**16d**
1	**1**	1	150	46	22
2	**1**	**0.5**	**150**	**58**	**14**
3	Pd(phen)(OAc)$_2$	0.5	150	57	29
4	Pd(phen)(tfa)$_2$	0.5	150	42	16
5	**1**	0.5	160	43	22
6	**1**	0.5	140	37	27
7[c]	**1**	0.5	150	74	not detected

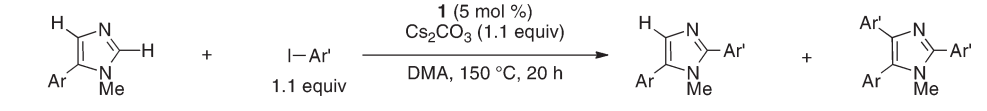
[a] The reactions were carried out with 0.25 mmol of **14b**. [b] Isolated yields. [c] Galvinoxyl (1 equiv) was used as an additive.

reacted sluggishly independent of the aryl iodide used, and as a result, longer times were needed to obtain satisfactory yields (entries 1−3). By using the new catalytic system, heteroaryl iodides, such as 2- or 3-pyridyl iodide, undergo coupling with imidazoles **14** (entries 10, 15). Sterically hindered 1-naphthyl and 2-tolyl iodide also react with imidazoles to give the corresponding arylated products **15h**, **15m**, and **15n** in moderate to high yields (entries 11, 16, 17). In addition, the presence of an *o*-methoxy group on the aryl halides, which can possibly bind to the catalyst, does not impede the reaction as demonstrated by the production of **15h** and **15n** in moderate to excellent yields (entries 12, 18). In this case also, the yields were improved when galvinoxyl is used as an additive (entries 1, 5, 6, 10, 13, 14). In addition, aryl bromides also underwent the reaction under the identical conditions to give the diarylated products in moderate yields, whereas the reaction of aryl chlorides did not proceed efficiently (*e.g.*, entry 4).

Direct C4 Arylation Reactions of 2,5-Diarylated *N*-Methylimidazoles. Most C4 arylation reactions of the azoles studied in the past have been promoted by using directing groups or substrate activation as shown in eq 2.[15,16] The reaction of 2,5-diphenyloxazole with bromobenzene, which affords the C4 arylated product, described by Fagnou was the sole example of a direct C4 arylation process.[16a] As a result of this lack of precedent, our attention turned to an investigation of C4 arylation reactions of azoles using $[Pd(phen)_2](PF_6)_2$ as the catalyst. The initial reactions were carried out with imidazole **15a**, 1.5 equiv of *p*-iodoanisole **5c**, and 10 mol % of catalyst **1**. As we expected, the C4 arylation process proceeded efficiently to give the triaryl product **17a** in quantitative yield (Table 5). The reaction took place even with *p*-bromoanisole instead of iodide **5c** though the yield of **17a** was moderate. In addition, reactions of several substrates bearing electron-donating and -withdrawing groups on the imidazole C2 and C5 aryl groups were carried out under these conditions with iodide **5**. The observations show that the new catalytic system is highly compatible with processes that yield adducts **17b**−**f** in good to excellent yields. Furthermore, this process can be used to couple the diphenyl-imidazole **6b** with the strong electron-withdrawing (*e.g.*, *p*-nitrophenyl, *p*-ethoxycarbonylphenyl) and electron-donating (*e.g.*, *p*-dimethylaminophenyl) group substituted iodides **5k**, **5l**, and **5m** to give the corresponding products **17g**, **17h**, and **17i** in good to high yields. Moreover, the reaction takes place when sterically crowded aryl iodide substrates are utilized, as exemplified by the reactions of **6b** with *o*-tolyl and 1-naphthyl iodides, **5j** and **5f**, respectively. In these cases the coupling product **17k** and **17l** are produced without significant loss of efficiency.

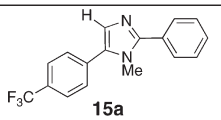
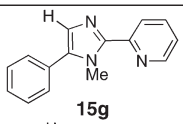
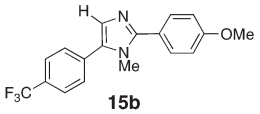
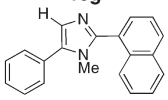
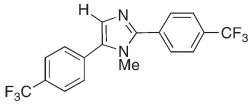
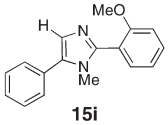
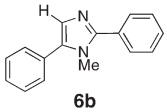
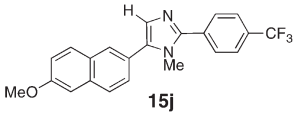
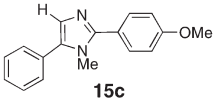
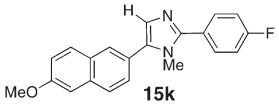
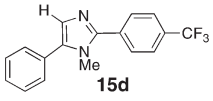
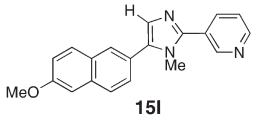
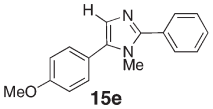
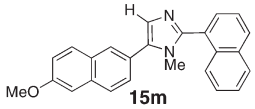
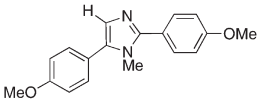
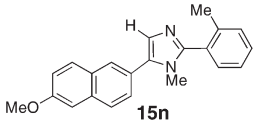
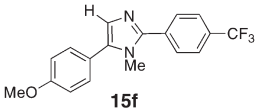
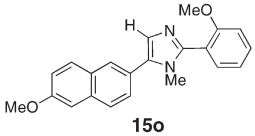
Sequential Arylation Reactions of Thiazole. Previously, Mori[8l,14c] and Fagnou[20] have observed excellent levels of selectivity in respective direct C2 and C5 monoarylation reactions of thiazole. We have also examined the applicability of the new catalytic system based on the palladium complex **1** to monoarylation reactions of thiazole. As the results shown in Scheme 2 indicate, C5 selective phenylation of thiazole occurs but only in a moderate yield (Conditions A). Therefore, the $Pd(OH)_2/C$ and KOAc system, described by Fagnou, was used to generate phenylthiazole **18** (Conditions B). In contrast, selective C2 arylation of **18** with *p*-anisyl iodide with catalyst **1** proceeds

Table 4. Scope of the Direct C2 Arylation Reactions of C5-Arylimazoles[a]



Ar = 4-$CF_3C_6H_4$-: **14a**; Ph-: **14b**; 4-$MeOC_6H_4$-: **14c**; 6-$MeOC_{10}H_6$-: **14d**

Ar' = 4-$CF_3C_6H_4$-: **5a**; Ph-: **5b**; 4-$MeOC_6H_4$-: **5c**; 6-$MeOC_{10}H_6$-: **5d**

entry	product	Yield[b] (%)	entry	product	Yield[b] (%)
1	 **15a**	31(9) 59(12)[c] [74(–)][d]	10	 **15g**	48(nd) [87(–)][d]
2	 **15b**	34(9) quant(–)[c]	11	 **15h**	69(nd)
3	 **6a**	36(14) 54(12)[e]	12	 **15i**	52(nd)
4	 **6b**	71(13) 57(12)[e] 7(trace)[f]	13	 **15j**	53(nd) [83(–)][d]
5	 **15c**	76(13) [85(–)][d]	14	 **15k**	59(nd) [93(–)][d]
6	 **15d**	58(14) [74(–)][d]	15	 **15l**	69(nd)
7	 **15e**	59(20) [52(nd[g])][d]	16	 **15m**	82(nd)
8	 **6c**	71(9)	17	 **15n**	68(nd)
9	 **15f**	55(19) [61(nd[g])][d]	18	 **15o**	92(nd)

[a] The reactions were carried out with 0.25 mmol of **14**. [b] Isolated yields. The yields of the triarylated byproduct are shown in parentheses. Also, nd in parentheses indicates not determined. [c] The reaction was carried out for 40 h. [d] Galvinoxyl (1 equiv) was used as an additive. [e] Phenylbromide was used as substrate instead of **5b**. [f] Phenylchloride was used as substrate instead of iodide **5b**. [g] Small amounts of the corresponding triarylated products were observed in the crude mixtures probably due to high reactivity of the substrates.

smoothly to give the diaryl-thiazole **19** in high yield. Earlier, we had observed that one-pot triarylation reactions of thiazole take place inefficiently and that the generated product mixtures contain predominantly diaryl-thiazoles (Table 1, entries 7−9). These findings show that C4 arylation reactions of thiazole **18** employing the new catalyst system are slow. In contrast, C4 arylation of the isolated diaryl-thiazole **19** occurred efficiently to give the triarylated product **20** in good yield.

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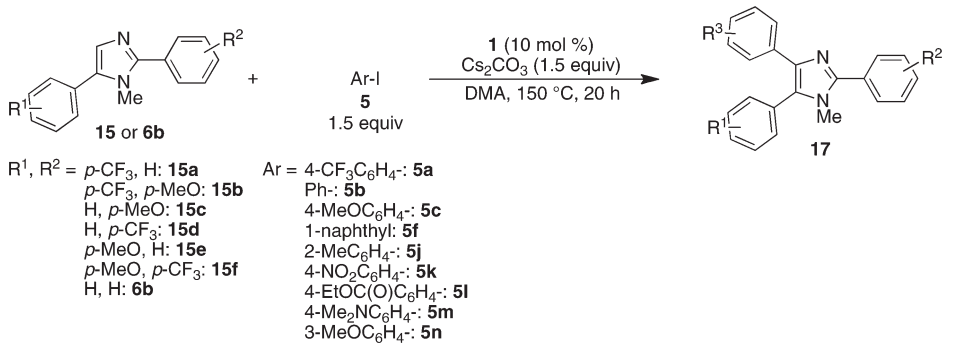
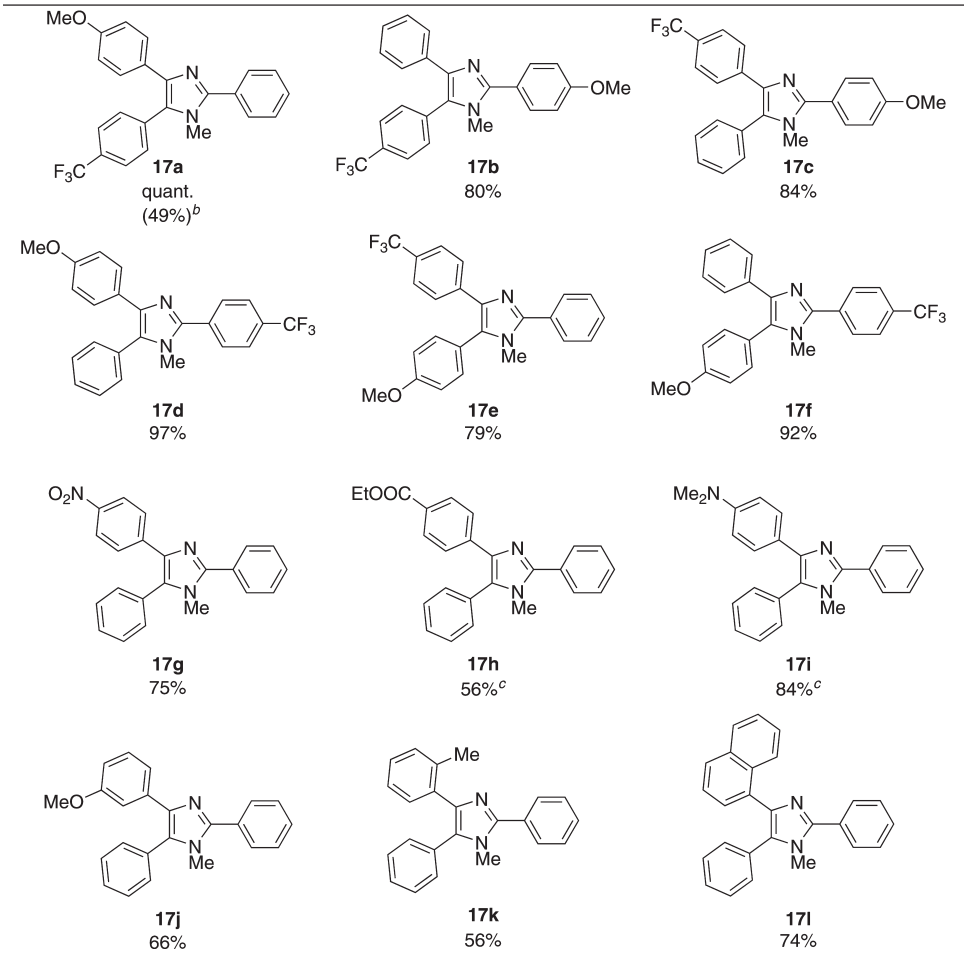
Table 5. Direct C4 Arylation Reactions of 2,5-Diaryl-*N*-methylimidazoles[a]





[a] The reactions were carried out with 0.125 mmol of **15** or **6b**. Isolated yields are shown. [b] Yield of the reaction with *p*-bromoanisole instead of **5c**. [c] K_2CO_3 (1.5 equiv) was used instead of Cs_2CO_3.

Mechanistic Studies of Direct Arylation Reactions Catalyzed by $[Pd(phen)_2](PF_6)_2$. Mechanisms for closely related direct C−H arylation reactions have been suggested to involve palladation of the aromatic components via electrophilic aromatic substitution (S_EAr) or concerted metalation-deprotonation (CMD) pathways in which carboxylates in the catalyst serve as the base (Scheme 3).[22] An alternative involving radical intemediates has been suggested (Scheme 4).[23−25] Although most of the recent examples of direct C−H arylation reactions can be understood in terms of the CMD pathway, this mechanism is not applicable to the system explored in this study since no carboxylates are present in the catalyst $[Pd(phen)_2](PF_6)_2$. In contrast to these proposals, we have previously suggested that, depending on the nature of the substrate, $[Pd(phen)_2](PF_6)_2$-promoted arylation reactions could proceed via radical pathways. This suggestion was based in part on the observed ortho, meta, and para product distributions that match those arising from known radical reactions between aryl iodides and an arenes.[18] In addition, operation of a radical pathway is consistent with the slight perturbation of the product distribution when galvinoxyl was added to the reaction mixture of benzoxazole (**21**) and **5a** (Scheme 5). Therefore, a radical pathway remains as a

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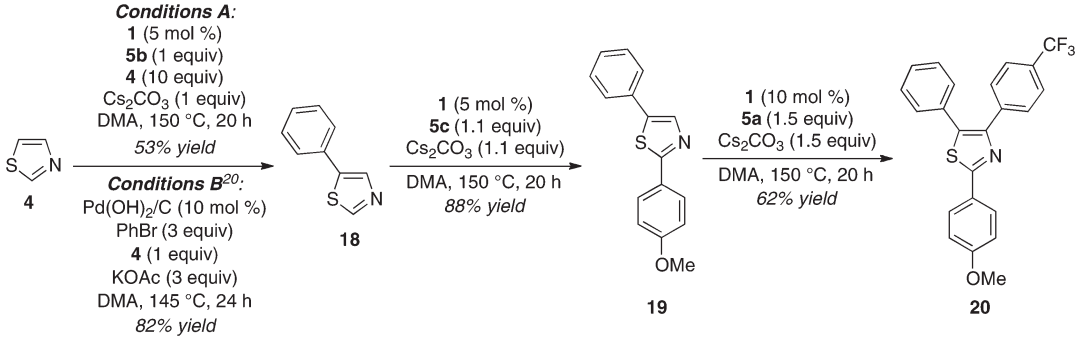
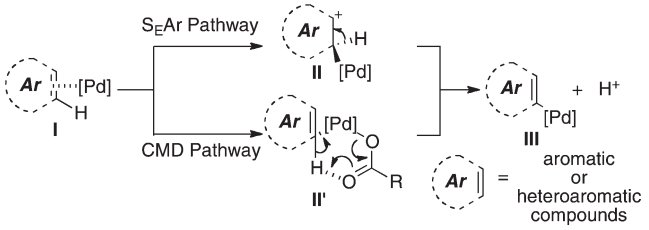
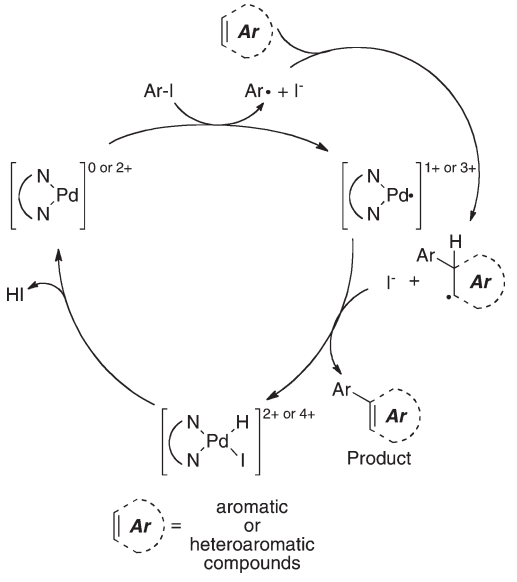
Scheme 2. Sequential Direct Arylation Reactions of Thiazole



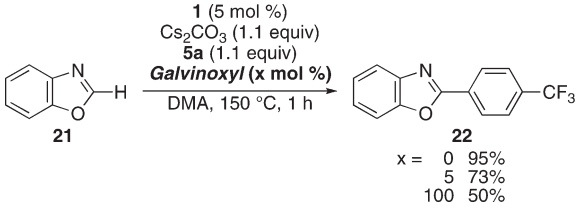
Scheme 3. Concise Mechanism for Palladation via the S_EAr Pathway and CMD Pathways



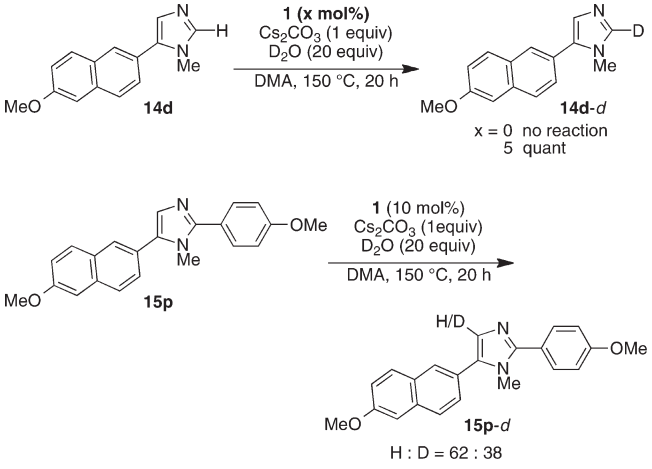
Scheme 4. Radical Mechanism for C4 Arylation



Scheme 5. Radical Trap Experiment on the Reaction of Benzoxazole (21)



Scheme 6. H−D Exchange Reactions Catalyzed by 1



plausible alternative for the reactions probed in this effort, even though it is known that radical scavengers like galvinoxyl can decompose[26] or ligate to[27] Pd complexes and influence their catalytic activities.

Another consideration is that the $[Pd(phen)_2](PF_6)_2$-catalyzed direct arylation reactions at three different azole positions could follow different mechanistic pathways. In order to gain additional information about the mechanism(s) of these pocesses and, in particular, those that take place at the C2 and C4 positions of azoles, several experiments were carried out. For example, when the C5-aryl-imidazole **14d** was treated with an excess of D_2O under the standard reaction conditions in the absence of an aryl halide, proton-exchange rapidly occurs at the C2 position to give monodeuterated **14d**-*d* quantitatively (Scheme 6, upper). Since this exchange reaction does not take place in the absence of catalyst **1**, it is clear that it is promoted by the palladium complex through a sequence involving S_EAr-type C2 palladation of the imidazole and protonolysis of the resulting Pd-imidazole intermediate.[28] Therefore, electrophilic palladation at C2 takes place smoothly to give Pd-aryl species (**III** in Scheme 3). In addition, the reaction of the relatively electron-deficient imidazole **14a** promoted by $[Pd(phen)_2](PF_6)_2$ takes

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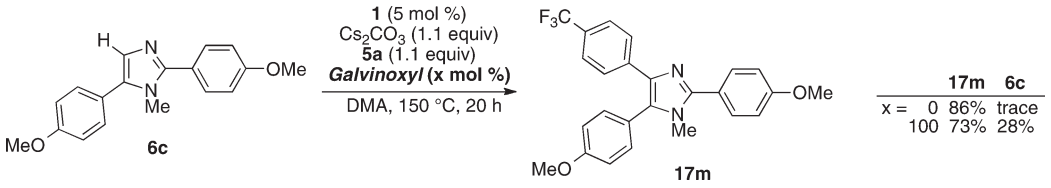
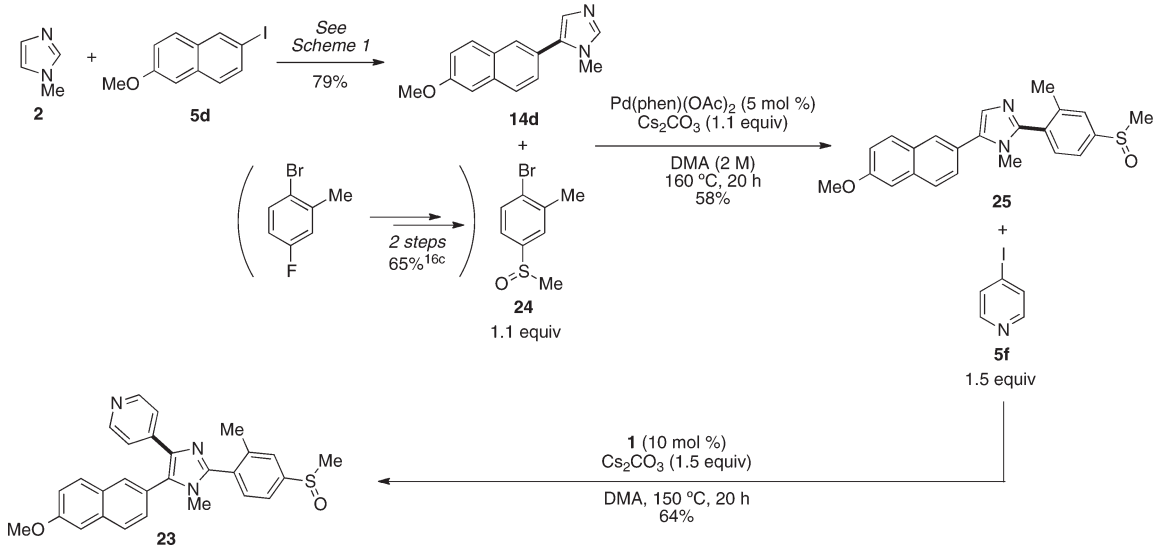
Scheme 7. Competitive Direct C4 Arylation Reactions of Diaryl-imidazoles[a]

[a] NMR yields. Isolated yields are shown in parentheses.

Scheme 8. Radical Trap Experiments of the Reaction of 6c



Scheme 9. Synthesis of Tie-2 Tyrosine Kinase Inhibitor (23)



place more slowly than those of its electron rich analogs (see Table 4, entries 1−3). On the basis of these results, it is likely that reactions of imidazoles with the catalyst take place preferentially at the C2 position via an S_EAr fashion.

In contrast, the H−D exchange reaction at the C4 position of the diaryl-imidazole **15p** proceeds much more slowly than the C2 exchange process (Scheme 6, lower). Also, reaction of a 1:1 mixture of the electron-deficient and electron-rich diaryl-imidazoles **6a** and **6c** with iodide **5a** affords almost equal amounts of the respective C4-arylated products **9a** and **17m** (Scheme 7). Furthermore, the C4 arylation process was inhibited to an observable degree by the radical trap galvinoxyl, yet C2 arylation reactions were not affected by this substance (Table 3, entries 7, 8 and Scheme 8). These observations suggest that reactions at C2 and C4 pass through different mechanistic pathways. The combined results appear to support the plausible conclusion that the palladation at C4 occurs by an electrophilic aromatic substitution route, whereas a radical pathway is followed in the reaction at C4. Further investigations are needed to elucidate fully the mechanism of the C4 arylation reactions.

Synthesis of the Tie-2 Tyrosine Kinase Inhibitor from *N*-Methylimidazole. To demonstrate the synthetic utility of the new arylation methodology, a synthesis of the medicinally important substance, the Tie-2 Tyrosine Kinase Inhibitor (**23**), was explored. The previous strategy employed to prepare **23** involves construction of the imidazole core by using a classical condensation strategy starting with fragments that already contain the requisite substituents in the target at C2, C4, and C5.[2] As a result, multistep syntheses of the fragments were needed. More recently, Fagnou developed a synthesis of **23** that relies on direct arylation of an imidazole *N*-oxide.[16c] In this case, owing to the instability of the imidazole core under oxidation conditions, the catalytic reactions were performed on the *N*-oxide of **14d**, which was synthesized by utilizing a classical condensation approach from a corresponding glyoxal oxime and 1,3,5-triazine.

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We envisioned that the three arene fragments present in **23** could be directly and sequentially installed starting with commercially available *N*-methylimidazole (**2**) by using the new catalytic arylation process (Scheme 9). Execution of a route following this plan began with the high yield preparation of the C5-aryl-imidazole **14d** from **2** by using the process shown in Scheme 1. In order to avoid diarylation at C2 and C4, coupling of **14d** with the relatively slowly reacting substrate, 2-methyl-4-methylsulfonylphenyl bromide (**24**),[16c] was attempted using **1** as the catalyst but the yield of the desired product **25** was low. A brief reinvestigation of the reaction conditions revealed that the use of $Pd(phen)(OAc)_2$ as a catalyst instead of **1** enables efficient and selective C2 arylation of **14d** with **24** to produce **25** in 58% yield. Finally, the target compound **23** was generated in pure form in 64% yield by reaction of **25** and 4-iodopyridine (**5f**). This three-step sequential arylation route for preparation of **23** takes place with an overall yield of 29%. To the best of our knowledge, this is the first example of a synthesis of **23** from commercially available **2** by using palladium-catalyzed direct C−H arylation reactions.

CONCLUSION

In the studies described above, we have developed an efficient direct C−H arylation reaction of simple azoles that is catalyzed by the 1,10-phenanthroline−Pd complex **1**. Although nitrogen-based ligands have rarely been used in catalysts that promote direct C−H arylation reactions, our efforts clearly reveal the significant potential of these types of catalysts. In fact, the catalytic system developed in this investigation even can be used to promote efficient direct C4 arylation reactions of simple azoles. Sequential arylations of simple azoles using the new catalytic system serves as the most simple and efficient method for preparation of triaryl-azoles bearing three different aryl groups. The advent of this versatile procedure for preparation of mono-, di-, and triaryl-azoles should enable wider screening and exploration of these potentially biological active substances. Further applications of the new catalytic system are being explored at the current time in our group.

EXPERIMENTAL SECTION

General. The ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$. Chemical shifts of ^{1}H and ^{13}C are reported in δ values referred to tetramethylsilane and $CDCl_3$ as an internal standard, respectively. The ^{19}F chemical shifts are expressed in δ values deshielded with respect to CF_3COOH as an external standard. The mass spectra (MS) and high resolution mass spectra (HRMS) were obtained by ionizing samples via electron ionization (70 eV).

Materials. Unless otherwise noted, reagents were commercially available and were used without purification. DMA was distilled over calcium hydride under reduced pressure. $Pd(phen)(OAc)_2$,[29] $Pd(phen)(OCOCF_3)_2$,[29] $[Pd(phen)_2](PF_6)_2$,[29] and **24**[16] were prepared according to the literature. Silica gel 60N (spherical, neutral, 40−50 mm) from Kanto Chemical Co., Inc. was used on flash column chromatography.

General Procedure for One-Pot Tri- or Diarylation of Azoles (Table 1 and eq 4). In a screw-capped test tube was placed Cs_2CO_3 (3 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then $Pd(phen)_2(PF_6)_2$ (5 mol %), azoles (0.5 mmol), aryliodides (3 equiv) and DMA (1 mL) were added. The resulting mixture was stirred under an Ar atmosphere at 150 °C for 40 h. The resulting mixture was filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was subjected to flash column chromatography to give the 2,5-di- and 2,4,5-triarylated products as white solids.

1-Methyl-2,4,5-tris(4-trifluoromethylphenyl)-1*H*-imidazole (9a).[18]. Yield 59%, white solid, R_f = 0.52 (hexane/AcOEt = 4:1). ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 3H), 7.51 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.79−7.80 (m, 4H), 7.91 (d, J = 8.0 Hz, 2H).

1-Methyl-2,5-bis(4-trifluoromethylphenyl)-1*H*-imidazole (6a).[18]. Yield 39%, white solid, R_f = 0.58 (*n*-Hex/EtOAc = 1:2). ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H), 7.32 (s, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.44−7.78 (m, 4H), 7.85 (d, J = 8.3 Hz, 2H).

1-Methyl-2,4,5-triphenyl-1*H*-imidazole (9b).[30]. Yield 61%, white solid, R_f = 0.58 (*n*-Hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 7.27 (t, J = 7.3 Hz, 1H), 7.24 (t, J = 7.3 Hz, 2H), 7.42−7.53 (m, 8H), 7.59 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 7.3 Hz, 2H).

1-Methyl-2,5-diphenyl-1*H*-imidazole (6b).[31]. Yield 31%, white solid, R_f = 0.35 (*n*-Hex/EtOAc = 1:2). ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 3H), 7.13 (s, 1H), 7.29−7.41 (m, 8H), 7.62 (d, J = 7.8 Hz, 2H).

1-Methyl-2,4,5-tris(4-methoxyphenyl)-1*H*-imidazole (9c). Yield 44%, white solid, mp 55−57 °C, R_f = 0.30 (DCM/MeOH = 100:3). IR (KBr) 2935, 2834, 1612, 1578, 1517, 1494, 1246 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.46 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 6.78 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 32.9, 55.1, 55.3, 55.3, 113.5, 113.9, 114.3, 114.4, 123.4, 127.4, 128.0, 128.9, 130.3, 132.1, 136.9, 147.3, 158.1, 159.6, 159.9. MS (EI) m/z: 400 (M^+). HRMS (EI): exact mass calcd for $C_{25}H_{24}N_2O_3$ (M^+); 400.1787. Found: 400.1786.

1-Methyl-2,5-bis(4-methoxyphenyl)-1*H*-imidazole (6c). Yield 40%, white solid, mp 204−207 °C, R_f = 0.10 (*n*-Hex/EtOAc = 1:1). IR (KBr) = 3010, 2954, 2933, 2835, 1612, 1576, 1553, 1249 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 6.99 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.11 (s, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.5, 55.3, 55.3, 113.9, 114.2, 122.8, 123.5, 126.6, 130.0, 130.1, 134.8, 148.8, 159.3, 159.9. MS (EI) m/z: 294 (M^+). HRMS (EI): exact mass calcd for $C_{18}H_{18}N_2O_2$ (M^+); 294.1368. Found: 294.1373.

2,4,5-Tris(4-trifluoromethylphenyl)oxazole (10a).[18]. Yield 76%, white solid, R_f = 0.34 (hexane/AcOEt = 10:1). ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 4H), 7.75−7.78 (m, 4H), 7.82 (d, J = 7.8 Hz, 2H), 8.25 (d, J = 8.3 Hz, 2H).

2,5-Bis(4-trifluoromethylphenyl)oxazole (7a).[18]. Yield 21%, white solid, R_f = 0.23 (hexane/AcOEt = 10:1). ^{1}H NMR ($CDCl_3$) δ 7.52 (s, 1H), 7.63−7.69 (m, 4H), 7.76 (d, J = 8.3 Hz, 2H), 8.15 (d, J = 8.3 Hz, 2H).

2,4,5-Triphenyloxazole (10b).[14b]. Yield 55%, white solid, R_f = 0.35 (hexane/AcOEt = 10:1). ^{1}H NMR ($CDCl_3$) δ 7.33−7.48 (m, 9H), 7.67 (d, J = 6.8 Hz, 2H), 7.72 (d, J = 7.3 Hz, 2H), 8.15 (d, J = 7.8 Hz, 2H).

2,5-Diphenyloxazole (7b).[8g]. Yield 34%, white solid, R_f = 0.22 (hexane/AcOEt = 10:1). ^{1}H NMR ($CDCl_3$) δ 7.32 (t, J = 7.3 Hz, 1H), 7.41−7.47 (m, 6H), 7.71 (d, J = 7.3 Hz, 2H), 8.11 (d, J = 6.8 Hz, 2H).

2,4,5-Tris(4-methoxyphenyl)oxazole (10c). Yield 49%, white solid, mp 140−142 °C, R_f = 0.23 (hexane/AcOEt = 4:1). IR (KBr) 3041, 2999, 1613, 1517, 1500, 1298, 1247, 1172, 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 6.84−6.93 (m, 4H), 6.97 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.2, 55.3, 55.3, 114.0, 114.2, 114.2, 120.4, 121.9, 125.3, 127.8, 127.9, 129.2, 135.1, 144.3, 159.3, 159.5, 159.6, 161.2. MS (EI) m/z: 387 (M^+). HRMS (EI): exact mass calcd for $C_{24}H_{21}NO_4$ (M^+); 387.1417. Found: 387.1413.

2,5-Bis(4-methoxyphenyl)oxazole (7c). Yield 30%, white solid, mp 105−107 °C, R_f = 0.23 (hexane/AcOEt = 4:1). IR (KBr) 1615, 1494, 1304, 1251, 1173, 1057, 1024, 951, 834, 820 cm^{-1}. ^{1}H NMR

($CDCl_3$) δ 3.80 (s, 3H), 3.83 (s, 3H), 6.91−6.95 (m, 4H), 7.23 (s, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.3, 55.3, 114.2, 114.3, 120.4, 121.0, 121.7, 125.5, 127.7, 150.7, 159.6, 160.6, 161.1. MS (EI) m/z: 281 (M^+). HRMS (EI): exact mass calcd for $C_{17}H_{15}NO_3$ (M^+); 281.1052. Found: 281.1043

2,5-Bis(4-trifluoromethylphenyl)thiazole (8a). Yield 73%, yellow solid, mp 155−156 °C, R_f = 0.20 (hexane/AcOEt = 10:1). IR (KBr) 1613, 1434, 1320, 1172, 1136, 1108, 1066, 835 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.56−7.62 (m, 6H), 7.96 (d, J = 8.3 Hz, 2H), 8.00 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 123.8 (q, J = 272.1 Hz, $F_3\underline{C}$), 123.9 (q, J = 272.1 Hz, $F_3\underline{C}$), 126.0 (q, J = 3.3 Hz, $F_3C-C{=}\underline{C}$), 126.2 (q, J = 3.3 Hz, $F_3C-C{=}\underline{C}$), 126.6, 126.8, 130.4 (q, J = 33.1 Hz, $F_3C-\underline{C}$), 131.0 (q, J = 33.1 Hz, $F_3C-\underline{C}$), 134.4, 136.4, 138.7, 140.7, 166.2. ^{19}F NMR ($CDCl_3$) δ −63.1, −63.2. MS (EI) m/z: 373 (M^+). HRMS (EI): exact mass calcd for $C_{17}H_9F_6NS$ (M^+); 373.0360. Found: 373.0349.

2,5-Diphenylthiazole (8b).[14b] Yield 93%yield, white solid, R_f = 0.24 (hexane/AcOEt = 10:1). ^{1}H NMR ($CDCl_3$) δ 7.31−7.47 (m, 6H), 7.59 (d, J = 7.8 Hz, 2H), 7.97 (d, J = 8.3 Hz, 2H), 8.02 (s, 1H).

2,5-Bis(4-methoxyphenyl)thiazole (8c).[8g] Yield 99%, yellow solid, R_f = 0.10 (hexane/AcOEt = 10:1). ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 3.84 (s, 3H), 6.91−6.95 (m, 4H), 7.49 (d, J = 8.1 Hz, 2H), 7.84−7.88 (m, 3 H).

1-Methyl-3,4,5-tris(4-trifluoromethylphenyl)pyrazole (13). Yield 52%, white solid, mp 156−157.5 °C, R_f = 0.62 (*n*-Hex/EtOAc = 4:1). IR (KBr) 3046, 2944, 1689, 1619, 1574, 1330 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 7.14 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.54−7.59 (m, 4H), 7.79 (d, J = 8.3 HZ, 2H). ^{13}C NMR ($CDCl_3$) δ 37.3, 118.4, 123.5 (q, J = 272.1 Hz, $F_3\underline{C}$), 123.8 (q, J = 272.1 Hz, $F_3\underline{C}$), 123.9 (q, J = 272.1 Hz, $F_3\underline{C}$), 125.1 (q, J = 3.3 Hz, $F_3C-C{=}\underline{C}$), 125.3 (q, J = 3.3 Hz, $F_3C-C{=}\underline{C}$), 125.6 (q, J = 3.3 Hz, $F_3C-C{=}\underline{C}$), 128.0, 128.9 (q, J = 33.1 Hz, $F_3C-\underline{C}$), 129.5 (q, J = 32.3 Hz, $F_3C-\underline{C}$), 130.2, 130.2, 130.9 (q, J = 32.3 Hz, $F_3C-\underline{C}$), 132.7, 136.0, 141.1, 147.2. One carbon atom was overlapped with a peak. ^{19}F NMR ($CDCl_3$) δ −62.9, −63.0, −63.3. MS (EI) m/z: 514 (M^+). HRMS (EI): exact mass calcd for $C_{25}H_{15}F_9N_2$ (M^+); 514.1092. Found: 514.1074.

General Procedure for the C5 Arylation of *N*-Methylimidazole (Table 2 and Scheme 1). In a screw-capped test tube was placed Cs_2CO_3 (1.1 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then $Pd(phen)_2(PF_6)_2$ (5 mol %), *N*-methylimidazole (10 equiv), aryliodides (0.5 mmol) and DMA (1 mL) were added. The resulting mixture was stirred under an Ar atmosphere at 150 °C for 20 h. The residue was subjected to flash column chromatography on silica gel to give the 5-arylated product as a white solid.

1-Methyl-5-(4-trifluoromethylphenyl)-1*H*-imidazole (14a).[19] Yield 74%, colorless oil, R_f = 0.10 (DCM/MeOH = 100:1). ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H), 7.18 (s, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.56 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H).

1-Methyl-5-phenyl-1*H*-imidazole (14b).[19] Yield 79%, brown solid, R_f = 0.10 (DCM/MeOH = 100:1). ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 7.11 (s, 1H), 7.37−7.44 (m, 5H), 7.53 (s, 1H).

1-Methyl-5-(4-methoxyphenyl)-1*H*-imidazole (14c).[19] Yield 86%, brown solid, R_f = 0.05 (DCM/MeOH = 100:1). ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 3H), 3.86 (s, 3H), 6.98 (d, J = 8.8 Hz, 2H), 7.05 (s, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.50 (s, 1H).

1-Methyl-5-(6-methoxy-2-naphthyl)-1*H*-imidazole (14d)[19]**.** Yield 81%, colorless solid, R_f = 0.07 (DCM/MeOH = 100:1). ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.96 (s, 3H), 7.17−7.22 (m, 3H), 7.48 (dd, J = 8.5 Hz, 1.7 Hz, 1H), 7.70 (s, 1H), 7.77−7.82 (m, 3H).

General Procedure for the C2 Arylation of 5-Arylazoles (Tables 3 and 4 and the Second Step of Sequential Arylation in Scheme 2). *Method I (No Additive).* In a screw-capped test tube was placed Cs_2CO_3 (1.1 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then $Pd(phen)_2(PF_6)_2$ (5 mol %), 5-arylaimidazoles (0.25 mmol), aryliodides (1.1 equiv) and DMA (1 mL) were added. The resulting mixture was stirred under an Ar atmosphere at 150 °C for 20−40 h. The residue was subjected to flash column chromatography on silica gel to give the 2,5-diarylated product as a white solid.

Method II (Addition of Galvinoxyl). In a screw-capped test tube was placed Cs_2CO_3 (1.1 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then $Pd(phen)_2(PF_6)_2$ (5 mol %), 5-arylaimidazoles (0.25 mmol), aryliodides (1.1 equiv), Galvinoxyl (1 equiv) and DMA (1 mL) were added. The resulting mixture was stirred under Ar atmosphere at 150 °C for 20 h. The residue was subjected to flash column chromatography on silica gel to give the 2,5-diarylated product as a white solid.

1-Methyl-2-phenyl-5-(4-trifluoromethylphenyl)-1*H*-imidazole (15a) (Method I). Yield 59%, white solid, mp 172−173 °C, R_f = 0.63 (*n*-Hex/EtOAc = 1: 2). IR (KBr) 2956, 1613. 1551, 1462, 1448, 1331 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H), 7.28 (s, 1H), 7.44−7.52 (m, 3H), 7.59 (d, J = 7.8 Hz, 2H), 7.69−7.73 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 33.9, 124.1 (q, J = 271.3 Hz, $\underline{C}F_3$), 125.8 (q, J = 3.3 Hz, $\underline{C}{=}C-CF_3$), 128.6, 128.6, 128.7, 128.9, 129.0, 129.8 (q, J = 33.1 Hz, $\underline{C}-CF_3$), 130.6, 133.9, 134.1, 150.5. ^{19}F NMR ($CDCl_3$) δ −62.9. MS (EI) m/z: 302 (M^+). HRMS (EI): exact mass calcd for $C_{17}H_{13}F_3N_2$ (M^+); 302.1031. Found: 302.1028.

1-Methyl-2-(4-methyoxyphenyl)-5-(4-trifluoromethylphenyl)-1*H*-imidazole (15b) (Method I). Quantitative yield, white solid, mp 177−179 °C, R_f 0.33 (*n*-Hex/EtOAc = 1: 2). IR (KBr) 2958, 2838, 1613, 1575, 1328, 1256 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.87 (s, 3H), 7.02 (d, J = 8.8 Hz, 2H), 7.27 (s, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.9, 55.3, 114.1, 123.0, 124.1 (q, J = 271.3 Hz, $\underline{C}F_3$), 125.7 (q, J = 3.3 Hz, $\underline{C}{=}C-CF_3$), 128.4, 128.4, 129.6 (q, J = 32.3 Hz, $\underline{C}-CF_3$), 130.3, 133.8, 134.0, 150.5, 160.3. ^{19}F NMR ($CDCl_3$) δ −62.9. MS (EI) m/z: 332 (M^+). HRMS (EI): exact mass calcd for $C_{18}H_{15}F_3N_2O$ (M^+); 332.1136. Found: 332.1115.

1-Methyl-2-(4-methoxyphenyl)-5-phenyl-1*H*-imidazole (15c) (Method II). Yield 85%, white solid, mp 176−177.5 °C, R_f = 0.23 (*n*-Hex/EtOAc = 1: 2). IR (KBr) 2953, 2834, 1612, 1577, 1252 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 3H), 3.85 (s, 3H), 7.00 (d, J = 9.1 Hz, 2H), 7.17 (s, 1H), 7.35−7.45 (m, 5H), 7.62 (d, J = 9.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.6, 55.2, 114.0, 123.4, 127.2, 127.7, 128.5, 128.7, 130.2, 130.4, 130.1, 149.4, 160.0. MS (EI) m/z: 264 (M^+). HRMS (EI): exact mass calcd for $C_{17}H_{16}N_2O$ (M^+); 264.1263. Found: 264.1269.

1-Methyl-2-(4-trifluoromethylphenyl)-5-phenyl-1*H*-imidazole (15d) (Method II). Yield 74%, white solid, mp 178−179 °C, R_f = 0.68 (*n*-Hex/EtOAc = 1: 2). IR (KBr) 3069, 2956, 1613, 1550, 1332 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H), 7.24 (s, 1H), 7.41−7.50 (m, 5H), 7.59 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.8, 55.3, 124.1 (q, J = 271.3 Hz, $\underline{C}F_3$), 125.6 (q, J = 3.3 Hz, $\underline{C}{=}C-CF_3$), 128.0, 128.1, 128.8, 128.9, 128.9, 129.8, 130.4 (q, J = 33.1 Hz, $\underline{C}-CF_3$), 134.4, 136.3, 147.8. ^{19}F NMR ($CDCl_3$) δ −63.0. MS (EI) m/z: 302 (M^+). HRMS (EI): exact mass calcd for $C_{17}H_{13}F_3N_2$ (M^+); 302.1031. Found: 302.1022.

1-Methyl-2-phenyl-5-(4-methoxyphenyl)-1*H*-imidazole (15e) (Method I). Yield 59%, white solid, mp 194−196 °C, R_f = 0.46 (*n*-Hex/EtOAc = 1:3). IR (KBr) 3058, 2952, 2834, 1610, 1575, 1248 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 3H), 3.86 (s, 3H), 7.00 (d, J = 8.8 Hz, 2H), 7.15 (s, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.43 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.3 Hz, 2H), 7.70 (d, J = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.5, 55.3, 114.0, 114.2, 122.7, 127.0, 128.5, 128.7, 130.2, 131.1, 135.2, 148.9, 159.5. MS (EI) m/z: 264 (M^+). HRMS (EI): exact mass calcd for $C_{17}H_{16}N_2O$ (M^+); 264.1263. Found 264.1261.

1-Methyl-2-(4-trifluoromethylphenyl)-5-(4-methyoxyphenyl)-1*H*-imidazole (15f) (Method II). Yield 61%, white solid, mp 185−186 °C, R_f = 0.38 (*n*-Hex/EtOAc = 1:3). IR (KBr) 2958, 1612, 1573, 1337, 1257 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 3.87 (s, 3H), 7.01 (d, J = 8.8 Hz, 2H), 7.18 (s, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.6, 55.3,

114.3, 122.2, 124.1 (q, J = 271.3 Hz, $\underline{C}F_3$), 125.6 (q, J = 3.3 Hz, $\underline{C}$=C−CF_3), 127.5, 128.8, 130.3 (Ar), 130.3 (q, J = 32.3 Hz, $\underline{C}$−CF_3), 134.5, 136.1, 147.4, 159.7. ^{19}F NMR ($CDCl_3$) δ −63.0. MS (EI) m/z: 332 (M^+). HRMS (EI): exact mass calcd for $C_{18}H_{15}F_3N_2O$ (M^+); 332.1136. Found: 332.1135.

1-Methyl-2-(2-pyridyl)-5-phenyl-1*H*-imidazole (15g) (Method II). Yield 87%, brown oil, R_f = 0.26 (*n*-Hex/EtOAc = 1:1). IR (neat) 2954, 1631, 1568, 1458, 1411 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 7.13−7.18 (m, 2H), 7.31−7.42 (m, 5H), 7.71 (t, J = 7.8 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.55 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 30.8, 122.5, 123.3, 127.7, 128.1, 128.8, 129.1*, 130.0, 136.7, 146.4, 148.3, 150.9. *Two carbon atoms are overlapped. MS (EI) m/z: 235 (M^+). HRMS (EI): exact mass calcd for $C_{15}H_{13}N_3$ (M^+); 235.1109. Found: 235.1103.

1-Methyl-2-(1-naphthyl)-5-phenyl-1*H*-imidazole (15h) (Method I). Yield 68%, yellow sticky oil, R_f = 0.38 (*n*-Hex/EtOAc = 1:1). IR (neat) 3050, 2949, 1644, 1603, 1550 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 3H), 7.39 (s, 1H), 7.46 (d, J = 6.8 Hz, 1H), 7.52−7.65 (m, 7H), 7.71 (d, J = 6.8 Hz, 1H), 7.90 (dd, J = 6.3, 4.4 Hz, 1H), 7.97−8.03 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 32.8, 125.1, 125.7, 126.2, 127.0, 127.6, 127.9, 128.4, 128.7, 128.8, 128.9, 129.0, 129.7, 130.4, 132.6, 133.7, 134.5, 148.1. MS (EI) m/z: 284 (M^+). HRMS (EI): exact mass calcd for $C_{20}H_{16}N_2$ (M^+); 284.1313. Found: 284.1307.

1-Methyl-2-(2-methoxyphenyl)-5-phenyl-1*H*-imidazole (15i) (Method I). Yield 52%, yellow sticky oil, R_f = 0.20 (*n*-Hex/EtOAc = 1:1). IR (neat) 3059, 2951, 2835, 1604, 1580, 1552, 1248 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H), 3.91 (s, 3H), 7.05 (d, J = 8.3 Hz, 1H), 7.12 (t, J = 7.3 Hz, 1H), 7.27 (s, 1H), 7.41 (dd, J = 7.3, 6.8 Hz, 1H), 7.47−7.54 (m, 5H), 7.58 (d, J = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 32.5, 55.5, 110.9, 120.4, 120.9, 127.5, 127.7, 128.6, 128.7, 130.6, 130.9, 132.5, 134.4, 147.2, 157.5. MS (EI) m/z: 264 (M^+). HRMS (EI): exact mass calcd for $C_{17}H_{16}N_2O$ (M^+); 264.1263. Found: 264.1269.

1-Methyl-2-(4-trifluoromethylphenyl)-5-(6-methoxyphenylnaphthyl)-1*H*-imidazole (15j) (Method II). Yield 83%, white solid, mp 222−224 °C, R_f = 0.43 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3031, 1629, 1455, 1338, 1269, 1123 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.91 (s, 3H), 7.14−7.16 (m, 2H), 7.27 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.70−7.84 (m, 7H). ^{13}C NMR ($CDCl_3$) δ 32.3, 55.7, 106.1, 120.0, 124.4 (q, J = 272.1 Hz, $\underline{C}F_3$), 125.2, 125.9 (q, J = 3.3 Hz, $\underline{C}$=C−CF_3), 127.4, 127.7, 128.0, 128.4, 129.1, 129.2, 129.9, 130.3 (q, J = 32.7 Hz, $\underline{C}$−CF_3), 134.5, 134.7, 136.8, 148.1, 158.7. ^{19}F NMR ($CDCl_3$) δ −63.3. MS (EI) m/z: 382 (M^+). HRMS (EI): exact mass calcd for $C_{22}H_{17}F_3N_2O$ (M^+); 382.1293. Found: 382.1295.

1-Methyl-2-(4-fluorophenyl)-5-(6-methoxy-2-naphthyl)-1*H*-imidazole (15k) (Method I). Yield 93%, white solid, mp 205−208 °C, R_f = 0.33 (*n*-Hex/EtOAc = 1:1). IR (KBr) 2957, 2840, 1628, 1602, 1550, 1452, 1246, 1216 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.96 (s. 3H), 7.17−7.23 (m, 4H), 7.27 (s, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.69−7.73 (m, 2H), 7.79 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.84 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 33.7, 55.3, 105.7, 115.7 (d, J = 21.5 Hz, F−C=$\underline{C}$), 119.6, 125.3, 127.1, 127.2 (d, J = 3.3 Hz, F−C=C−C=$\underline{C}$), 127.3, 127.4, 127.6, 128.8, 129.6, 130.7 (d, J = 9.1 Hz, F−C=C−$\underline{C}$), 134.0, 135.7, 148.5, 158.2, 163.1 (d, J = 249.0 Hz, F−$\underline{C}$). ^{19}F NMR ($CDCl_3$) δ −112.7. MS (EI) m/z: 332 (M^+). HRMS (EI): exact mass calcd for $C_{21}H_{17}FN_2O$ (M^+); 332.1325. Found: 332.1328.

1-Methyl-2-(3-pyridyl)-5-(6-methoxy-2-naphthyl)-1*H*-imidazole (15l) (Method I). Yield 69%, white solid, mp 186−187 °C, R_f = 0.05 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3038, 2957, 2844, 1630, 1606, 1572, 1262 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.95 (s. 3H), 7.18 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 8.8, 2.4 Hz, 1H), 7.32 (s, 1H), 7.43 (dd, J = 8.8, 4.4 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.84 (s, 1H), 8.09 (d, J = 8.3 Hz, 1H), 8.67 (brs, 1H), 9.00 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 33.8, 55.3, 105.7, 119.6, 123.6, 124.9, 127.0, 127.3, 127.4, 127.7, 128.3, 128.8, 129.6, 134.1, 136.1, 136.4, 146.3, 149.3, 149.6, 158.3. MS (EI) m/z: 315 (M^+). HRMS (EI): exact mass calcd for $C_{20}H_{17}N_3O$ (M^+); 315.1372. Found: 315.1377.

1-Methyl-2-(1-naphthyl)-5-(6-methoxy-2-naphthyl)-1*H*-imidazole (15m) (Method I). Yield 82%, white solid, mp 146−148 °C, R_f = 0.35 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3050, 3001, 2936, 2840, 1629, 1606, 1560, 1261 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3H), 3.96 (s, 3H), 7.20 (m, 2H), 7.43 (s, 1H), 7.54−7.63 (m, 4H), 7.79 (d, J = 5.9 Hz, 1H), 7.81−8.00 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 32.9, 55.3, 105.7, 119.5, 125.1, 125.5, 125.7, 126.2, 127.0, 127.1, 127.3, 127.4, 127.7, 128.4, 128.7, 128.9, 129.3, 129.6, 129.7, 132.5, 133.7, 133.9, 134.7, 148.0, 158.2. MS (EI) m/z: 364 (M^+). HRMS (EI): exact mass calcd for $C_{25}H_{20}N_2O$ (M^+); 364.1576. Found: 364.1565.

1-Methyl-2-(2-methylphenyl)-5-(6-methoxynaphthyl)-1*H*-imidazole (15n) (Method I). Yield 68%, white solid, mp 122−123 °C, R_f = 0.40 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3057, 1605, 1450, 1260, 1244, 1024 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.67 (s, 3H), 3.92 (s, 3H), 7.14−7.19 (m, 3H), 7.24−7.38 (m, 3H), 7.53 (t, J = 8.4 Hz, 1H), 7.67 (dd, J = 8.4 Hz, 5.2 Hz, 1H), 7.74−7.82 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 19.7, 32.4, 55.3, 105.7, 119.5, 125.6, 125.7, 127.1, 127.2, 127.2, 127.9, 128.8, 129.3, 129.5, 130.4, 130.6, 130.9, 133.9, 134.0, 138.4, 148.9, 158.1. MS (EI) m/z: 328 (M^+). HRMS (EI): exact mass calcd for $C_{22}H_{20}N_2O$ (M^+); 328.1576. Found: 328.1576.

1-Methyl-2-(2-methoxyphenyl)-5-(6-methoxynaphthyl)-1*H*-imidazole (15o) (Method I). Yield 92%, white solid, mp 159−161 °C, R_f = 0.13 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3026, 1606, 1470, 1449, 1259, 1021 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.54 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 7.03 (d, J = 7.8 Hz, 1H), 7.09 (dd, J = 7.8, 7.3 Hz, 1H), 7.19−7.22 (m, 2H), 7.30 (s, 1H), 7.46 (dd, J = 8.3, 7.5 Hz, 1H), 7.55−7.59 (m, 2H), 7.78−7.87 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 32.3, 55.0, 55.2, 105.4, 110.6, 119.1, 120.1, 120.6, 125.4, 126.8, 126.9, 126.9, 127.2, 128.5, 129.2, 130.5, 132.2, 133.5, 134.2, 146.8, 157.2, 157.7. MS (EI) m/z: 344 (M^+). HRMS (EI): exact mass calcd for $C_{22}H_{20}N_2O_2$ (M^+); 344.1525. Found: 344.1522.

1-Methyl-2-(2-methoxyphenyl)-5-(6-methoxynaphthyl)-1*H*-imidazole (15p) (Method I). Yield 68%, white solid, mp 200−202 °C, R_f = 0.38 (*n*-Hex/EtOAc = 1:1). IR (KBr) 2951, 1604, 1452, 1251, 1025 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3H), 3.77 (s, 3H), 3.85 (s, 3H), 6.92 (d, J = 8.8 Hz, 2H), 7.08−7.13 (m, 2H), 7.17 (s, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.68−7.76 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 33.5, 55.0, 105.3, 113.7, 119.1, 123.2, 125.2, 126.7, 126.9, 128.5, 129.1, 129.6, 129.9, 132.0, 133.6, 135.0, 149.0, 157.8, 159.6. MS (EI) m/z: 344 (M^+). HRMS (EI): exact mass calcd for $C_{22}H_{20}N_2O_2$ (M^+); 344.1524. Found: 344.1511.

General Procedure for the C4 Arylation of 2,5-Diarylazoles (Table 5 and the Third Step of Sequential Arylation in Scheme 2). In a screw-capped test tube was placed Cs_2CO_3 (1.5 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then $Pd(phen)_2(PF_6)_2$ (5 mol %), 2,5-diarylazole (0.25 mmol), aryliodide (1.5 equiv) and DMA (0.5 mL) were added. The resulting mixture was stirred under Ar atmosphere at 150 °C for 20 h. The residue was subjected to flash column chromatography on silica gel to give the 2,4,5-triarylated product **17** or **23**.

1-Methyl-2-phenyl-4-(4-methoxyphenyl)-5-(4-trifluoromethylphenyl)-1*H*-imidazole (17a). Quantitative yield, white solid, mp 130−131 °C, R_f = 0.45 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3068, 2973, 2937, 1614, 1575, 1322 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H), 3.79 (s, 3H), 6.79 (d, J = 8.8 Hz, 2H), 7.43−7.56 (m, 7H), 7.74 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 33.3, 55.1, 113.7, 124.1 (q, J = 272.1 Hz, $\underline{C}F_3$), 126.0 (q, J = 4.1 Hz, $\underline{C}$=C−CF_3), 126.9, 128.0, 128.5, 128.7, 129.0, 129.1, 130.3 (q, J = 33.1 Hz, $\underline{C}$−CF_3), 130.7, 131.2, 135.1, 138.7, 148.6, 158.6. ^{19}F NMR ($CDCl_3$) δ −63.0. MS (EI) m/z: 408 (M^+). HRMS (EI): exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M^+); 408.1449. Found: 408.1447.

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1-Methyl-2-(4-methoxyphenyl)-4-phenyl-5-(4-trifluoromethylphenyl)-1*H*-imidazole (17b). Yield 80%, white solid, mp 192−193 °C, R_f = 0.45 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3071, 2999, 2965, 2935, 2836, 1576, 1470, 1332, 1253 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.51 (s, 3H), 3.88 (s, 3H), 7.04 (d, J = 8.8 Hz, 2H), 7.19−7.25 (m, 3H), 7.51 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.3, 55.3, 114.1, 123.1, 124.1 (q, J = 272.1 Hz, $\underline{C}F_3$), 125.9 (q, J = 3.3 Hz, $\underline{C}$=C−CF_3), 126.7, 127.3, 128.3, 128.6, 130.1 (q, J = 32.3 Hz, $\underline{C}$−CF_3), 130.5, 131.1, 134.3, 135.1, 138.6, 148.8, 160.3. ^{19}F NMR ($CDCl_3$) δ −63.0. MS (EI) m/z: 408 (M^+). HRMS (EI): exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M^+); 408.1449. Found: 408.1457.

1-Methyl-2-(4-methoxyphenyl)-4-(4-trifluoromethylphenyl)-5-phenyl-1*H*-imidazole (17c). Yield 84%, white solid, mp 196−197 °C, R_f = 0.45 (*n*-Hex/EtOAc = 1:1). IR (KBr) 2938, 2840, 1616, 1578, 1322, 1251 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.49 (s, 3H), 3.88 (s, 3H), 7.04 (d, J = 8.8 Hz, 2H), 7.41−7.52 (m, 7H), 7.64−7.69 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 33.0, 55.3, 114.1, 123.1, 124.5 (q, J = 272.1 Hz, $\underline{C}F_3$), 125.0 (q, J = 4.1 Hz, $\underline{C}$=C−CF_3), 126.7, 128.9 (q, J = 32.3 Hz, $\underline{C}$−CF_3), 129.0, 129.3, 130.5, 130.8, 130.9, 131.4, 136.1, 138.3, 148.3, 160.3. ^{19}F NMR ($CDCl_3$) δ −58.0. MS (EI) m/z: 408 (M^+). HRMS (EI): exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M^+); 408.1449. Found: 408.1459.

1-Methyl-2-(4-trifluoromethylphenyl)-4-(4-methoxyphenyl)-5-phenyl-1*H*-imidazole (17d). Yield 97%, white solid, mp 162−165 °C, R_f = 0.60 (*n*-Hex/EtOAc = 1:1). IR (KBr) 2937, 2841, 1617, 1578, 1322, 1251 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.54 (s, 3H), 3.77 (s, 3H), 6.79 (d, J = 9.0 Hz, 2H), 7.40−7.50 (m, 7H), 7.76 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.2, 55.1, 113.6, 123.7 (q, J = 272.1 Hz, $\underline{C}F_3$), 125.5 (q, J = 3.3 Hz, $\underline{C}$=C−CF_3), 127.1, 128.1, 128.7, 129.1, 129.1, 130.4, 130.5 (q, J = 33.1 Hz, $\underline{C}$−CF_3), 130.9, 131.0, 134.5, 138.2, 146.2, 158.5. ^{19}F NMR ($CDCl_3$) δ −63.0. MS (EI) m/z: 408 (M^+). HRMS (EI): exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M^+); 408.1449. Found: 408.1447.

1-Methyl-2-phenyl-4-(4-trifluoromethylphenyl)-5-(4-methoxyphenyl)-1*H*-imidazole (17e). Yield 79%, white solid, mp 167−169 °C, R_f = 0.45 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3070, 3009, 2962, 2938, 1616, 1562, 1322, 1251 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.50 (s, 3H), 3.90 (s, 3H), 7.05 (d, J = 8.8 Hz, 2H), 7.34 (d, J =8.3 Hz, 2H), 7.44−7.53 (m, 5H), 7.70 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 32.9, 55.3, 114.8, 122.8, 124.5 (q, J = 272.1 Hz, $\underline{C}F_3$), 125.0 (q, J = 3.3 Hz, $\underline{C}$=C−CF_3), 126.0, 127.7 (q, J = 32.3 Hz, $\underline{C}$−CF_3), 128.7, 129.0, 129.0, 130.8, 131.5, 132.1, 136.2, 138.4, 148.1, 160.2. ^{19}F NMR ($CDCl_3$) δ −62.6. MS (EI) m/z: 408 (M^+). HRMS (EI): exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M^+); 408.1449. Found: 408.1442.

1-Methyl-2-(4-trifluoromethylphenyl)-4-phenyl-5-(4-methoxyphenyl)-1*H*-imidazole (17f). Yield 92%, white solid, mp 146−147 °C, R_f = 0.45 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3070, 3020, 2938, 2841, 2938, 2841, 1613, 1600, 1572, 1326, 1251 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.54 (s, 3H), 3.90 (s, 3H), 7.04 (d, J = 8.8 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 7.25 (t, J = 7.3 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 7.3 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.91 (d, J = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.1, 55.3, 114.6, 122.9, 124.1 (q, J = 272.1 Hz, $\underline{C}F_3$), 125.6 (q, J = 3.3 Hz, $\underline{C}$=C−CF_3), 126.5, 126.8, 128.2, 129.1, 130.3 (q, J = 32.3 Hz, $\underline{C}$−CF_3), 131.1, 132.1, 134.5, 134.6, 138.3, 146.1, 160.0. ^{19}F NMR ($CDCl_3$) δ −63.0. MS (EI) m/z: 408 (M^+). HRMS (EI): exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M^+); 408.1449. Found: 408.1442.

1-Methyl-2,5-diphenyl-4-(4-nitrophenyl)-1*H*-imidazole (17g). Yield 75%, yellow solid, mp 207−209 °C, R_f = 0.20 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3057, 2950, 1594, 1558, 1508, 1382, 1321, 853 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.50 (s, 3H), 7.40−7.54 (m, 8H), 7.69 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 6.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.1, 123.5, 126.7, 128.7, 129.0, 129.2, 129.3, 129.4, 130.3, 130.4, 130.6, 132.9, 135.5, 141.3, 145.8, 148.6. MS (EI) m/z: 355 (M^+); HRMS (EI): calcd for $C_{22}H_{17}N_3O_2$ (M^+); 355.1321. Found: 355.1334.

1-Methyl-2,5-diphenyl-4-(4-ethoxycarbonylphenyl)-1*H*-imidazole (17h). Yield 56%, yellow solid, mp 122−122.5 °C, R_f = 0.25 (*n*-Hex/EtOAc = 1:1). IR (KBr) 3058, 2979, 1709, 1508, 1474, 1323, 1270, 1097, 859 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.35 (t, J = 7.3 Hz, 3H), 3.50 (s, 3H), 4.34 (q, J = 7.3 Hz, 2H), 7.39−7.52 (m, 8H), 7.62 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 6.8 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 14.3, 33.1, 60.6, 126.1, 127.6, 128.3, 128.4, 128.7, 128.9, 128.9, 129.1, 130.4, 130.4, 130.5, 131.4, 136.4, 138.9, 147.9, 166.4. MS (EI) m/z: 382 (M^+); HRMS (EI): calcd for $C_{25}H_{22}N_2O_2$ (M^+); 382.1681. Found: 382.1689.

1-Methyl-2,5-diphenyl-4-(4-*N*,*N*-dimethylaminophenyl)-1*H*-imidazole (17i). Yield 84%, white solid, mp 144−145 °C, R_f = 0.13 (*n*-Hex/EtOAc = 4:1). IR (KBr) 3056, 2923, 2798, 1615, 1514, 1348, 1194 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.84 (s, 6H), 3.43 (s, 3H), 6.55 (d, J = 8.8 Hz, 2H), 7.35−7.44 (m, 10 H), 7.68 (d, J = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 30.0, 40.5, 112.3, 127.8, 128.3, 128.5, 128.6, 128.8, 128.9, 128.9, 129.1, 129.3, 131.1, 131.7, 138.1, 147.5, 149.2. MS (EI) m/z: 353 (M^+); HRMS (EI): calcd for $C_{24}H_{23}N_3$ (M^+); 353.1892. Found: 353.1900.

1-Methyl-2,5-diphenyl-4-(3-methoxyphenyl)-1*H*-imidazole (17j). Yield 66%, colorless sticky oil, R_f = 0.25 (*n*-Hex/EtOAc = 1:1). IR (neat) 3056, 2932, 2832, 1601, 1238, 1043 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.51 (s, 3H), 3.66 (s. 3H), 6.73 (ddd, J = 7.8, 2.7, 1.5 Hz, 1H), 7.11−7.18 (m, 3H), 7.43−7.53 (m, 8H), 7.77 (d, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.0, 54.9, 114.5, 112.9, 119.4, 128.5, 128.6, 128.6, 128.8, 129.0, 129.1, 130.6, 130.8, 130.9, 131.2, 135.9, 137.5, 147.8, 159.4. MS (EI) m/z: 340 (M^+); HRMS (EI): calcd for $C_{23}H_{20}N_2O$ (M^+); 340.1576. Found: 340.1570.

1-Methyl-2,5-diphenyl-4-(2-methylphenyl)-1*H*-imidazole (17k). Yield 56%, white solid, mp 50−51 °C, R_f = 0.39 (*n*-Hex/EtOAc = 1:1). IR (KBr) 2921, 1601, 1498, 1469, 1377, 1073 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.21 (s, 3H), 3.72 (s, 3H), 7.12−7.18 (m, 2H), 7.30−7.55 (m, 10H), 7.83 (d, J = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 20.3, 33.9, 125.2, 127.1, 127.4, 127.6, 128.4, 128.6, 128.9, 129.9, 130.1, 130.7, 130.8, 130.9, 131.5, 134.4, 137.0, 139.1, 147.8. MS (EI) m/z: 324 (M^+); HRMS (EI): calcd for $C_{23}H_{20}N_2$ (M^+); 324.1626. Found: 324.1624.

1-Methyl-2,5-diphenyl-4-(1-naphthyl)-1*H*-imidazole (17l). Yield 78%, white solid, mp 95−96 °C, R_f = 0.25 (*n*-Hex/EtOAc = 4:1). IR (KBr) 3053, 2952, 1470, 1374, 1314, 771, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.72 (s, 3H), 7.26−7.52 (m, 12H), 7.74−7.84 (m, 4H), 8.30 (d, J = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 34.0, 125.1, 125.4, 125.7, 126.7, 127.5, 127.8, 127.9, 128.4, 128.5, 128.5, 128.7, 129.0, 129.1, 130.1, 139.3, 130.9, 132.4, 132.6, 133.9, 138.1, 148.0. MS (EI) m/z: 360 (M^+); HRMS (EI): calcd for $C_{26}H_{20}N_2$ (M^+); 360.1626. Found: 360.1615.

1-Methyl-2,5-bis(4-methoxyphenyl)-4-(4-trifluoromethylphenyl)-1*H*-imidazole (17m). Yield 86%, white solid, mp 65−66 °C, R_f = 0.43 (*n*-Hex/EtOAc = 1:1). IR (KBr) 2932, 1616, 1495, 1324, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.46 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 7.01−7.04 (m, 4H), 7.31 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.65−7.69 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 32.3, 54.9, 55.0, 113.8, 114.4, 122.5, 122.9, 124.2 (q, J = 271.3 Hz, $\underline{C}F_3$), 124.7 (q, J = 3.3 Hz, $\underline{C}$=C−CF_3), 126.2, 127.7 (q, J = 32.3 Hz, $\underline{C}$−CF_3), 130.1, 130.9, 131.7, 135.6, 138.2, 147.7, 159.8, 159.9. ^{19}F NMR ($CDCl_3$) δ −62.6. MS (EI) m/z: 438 (M^+). HRMS (EI): exact mass calcd for $C_{25}H_{21}F_3N_2O_2$ (M^+); 438.1555. Found: 438.1553.

5-Phenylthiazole (18).[32] Yield 53%, yellow solid, R_f = 0.22 (*n*-Hex/EtOAc = 4:1). ^1H NMR ($CDCl_3$) δ 7.35−7.44 (m, 3H), 7.59 (d, J = 9.3 Hz, 2H), 8.09 (s, 1H), 8.76 (s, 1H).

2-(4-Methoxyphenyl)-5-phenylthiazole (19)[33] **(Method I).** Yield 88%, white solid, R_f = 0.50 (*n*-Hex/EtOAc = 3:1). ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 6.98 (d, J = 8.8 Hz, 2H), 7.32 (t, J = 7.3 Hz,

1H), 7.42 (dd, J = 7.8, 7.3 Hz, 2H), 7.60 (d, J = 7.8 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H), 7.98 (s, 1H).

2-(4-Methoxyphenyl)-4-(4-trifluoromethylphenyl)-5-phenylthiazole (20). Yield 62%, white solid, mp 95−97 °C, R_f = 0.50 (n-Hex/EtOAc = 10:1). IR (KBr) 3027, 2937, 2835, 1607, 1575, 1324, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 7.00 (d, J = 9.3 Hz, 2H), 7.36−7.40 (m, 5H), 7.56 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.4, 113.6, 124.1 (q, J = 272.1 Hz, $\underline{C}F_3$), 125.2 (q, J = 3.3 Hz, $\underline{C}$=C−CF_3), 126.4, 128.0, 128.5, 129.0, 129.3, 129.6 (q, J = 32.7 Hz, $\underline{C}$−CF_3), 129.7, 131.7, 133.7, 138.6, 148.9, 161.4, 166.0. ^{19}F NMR ($CDCl_3$) δ −62.9. MS (EI) m/z: 438 (M^+). HRMS (EI) m/z: exact mass calcd for $C_{23}H_{16}F_3NOS$ (M^+); 411.0905. Found: 411.0905.

Intermediates of the Synthesis of Tie-2 (Scheme 9). *1-Methyl-2-(4-methanesulfinyl-2-methylphenyl)-5-(6-methoxynaphthalen-2-yl)-1H-imidazole (**25**).* Yield 58%, white solid. mp 190.5−191.5 °C, R_f = 0.05 (DCM/MeOH = 100:1). IR (KBr) 2926, 2865, 1733, 1632, 1507, 1456, 1352, 1251, 1135, 1011, 903 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.78 (s, 3H), 3.52 (s, 3H), 3.95 (s, 3H), 7.18−7.19 (m, 1H), 7.21 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.31 (s, 1H), 7.54 (dd, J = 8.8, 2.0 Hz, 1H), 7.56−7.58 (m, 2H), 7.66 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.82−7.85 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 20.0, 32.6, 43.8, 55.3, 105.6, 119.5, 120.7, 125.0, 125.2, 126.9, 127.2, 127.3, 127.3, 128.6, 129.4, 131.4, 133.5, 133.9, 134.4, 140.1, 146.5, 147.2, 158.1. MS (EI) m/z: 390 (M^+). HRMS (EI): exact mass calcd for $C_{23}H_{22}N_2O_2S$ (M^+); 390.1402. Found: 390.1404.

*1-Methyl-2-(4-methanesulfinyl-2-methylphenyl)-4-(4-pyridyl)-5-(6-methoxynaphthalen-2-yl)-1H-imidazole (**23**).*[16] Yield 64%, yellow solid, R_f = 0.35 (MeOH/hexane = 1:10). ^1H NMR ($CDCl_3$) δ2.48 (s, 3H), 2.77 (s, 3H), 3.32 (s, 3H), 3.98 (s, 3H), 7.24−7.27 (m, 2H), 7.44−7.46 (m, 3H), 7.58 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.68 (s, 1H), 7.79 (d, J = 9.8 Hz, 1H), 7.86 (s, 1H), 7.91 (d, J = 8.3 Hz, 1H), 8.36 (d, J = 5.9 Hz, 2H).

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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