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One-pot Sequential Direct C−H Bond Arylation of Azoles Catalyzed by $[Pd(phen)_2](PF_6)_2$: Synthetic Methods for Triarylated Azoles

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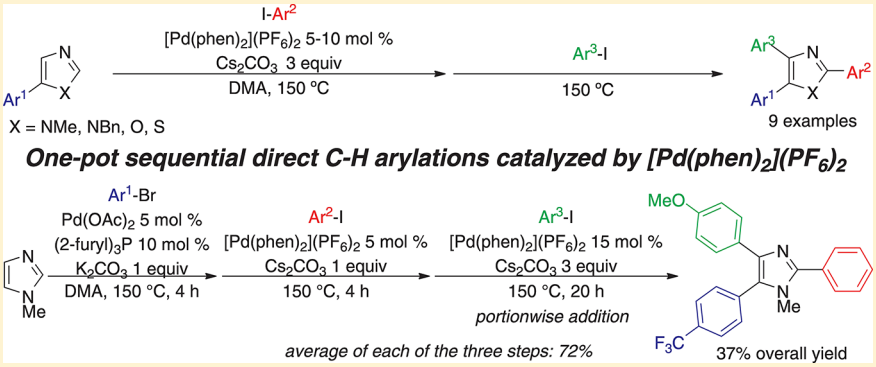
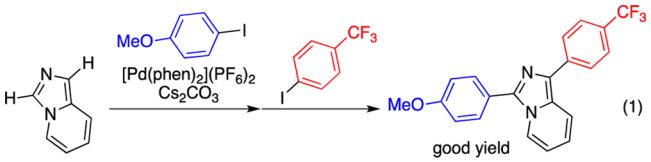
Supporting Information



ABSTRACT: Synthetic methods for triarylated azoles containing three different aryl groups via one-pot sequential multiple C−H bond arylations are described. The one-pot sequential diarylation of C5-monoarylated azoles was achieved by the simple sequential addition of two different aryl iodides with a $[Pd(phen)_2]PF_6$ catalytic system. The one-pot triarylation of *N*-methylimidazole was achieved by the combination of a previously reported $Pd(OAc)_2$−$P(2\text{-furyl})_3$ system and the present $[Pd(phen)_2]PF_6$ system. In this case, portionwise addition of aryl halide, base and the catalyst in the final step significantly improved the overall yield of the desired triarylated product. These protocols led to triarylated azoles without a loss of efficiency compared to the corresponding previously reported stepwise syntheses via direct C−H bond arylation.

Polyarylated azole structures are frequent constituents of natural products, functional materials, and pharmaceuticals, and their synthesis has been extensively studied for over a century.[1] Classically, such multifunctionalized azole derivatives have been obtained by the condensation-cyclization of carbonyl compounds and nitrogen-containing compounds,[2] but these methods require substrates in which the desired functional groups are incorporated at the early stage of the synthesis. Thus, the entire synthesis has to be repeated to obtain diverse derivatives. In contrast, those with aryl groups can be directly introduced to the parent azole frameworks in the late stage of the synthesis by the cross-coupling reactions of organometallic reagents and halides.[3] These methods lead to a variety of arylated azoles in a short step from common platforms. However, some issues still remain, such as the generation and stability of the corresponding azole metallic species.[4] Meanwhile, direct C−H arylation has recently emerged as an alternative to cross-coupling reactions since it does not require labile azole metallic species.[5,6] In this context, we have developed multiple arylation reactions of azoles with aryl halides catalyzed by Pd-phenanthroline complexes such as $[Pd(phen)_2](PF_6)_2$ (phen = 1,10-phenanthroline).[7] This reaction does not require stoichiometric amounts of organometallic reagents. More importantly, the stepwise operation of a similar catalytic reaction allows for the incorporation of three different aryl groups at all three C−H bonds in azoles. We then envisioned the use of our catalytic system for the multiple C−H bond arylation of azoles with different aryl iodides in one-pot as a time-integration approach,[8,9] which would make it possible to avoid chromatographic purification in each step. Recently, we reported the diarylation of the azole derivative imidazo[1,5-*a*]pyridine with this one-pot multiple arylation strategy (eq 1).[10] As a result, diarylation proceeded without a significant loss



of efficiency compared to a conventional stepwise method. We report here the further investigation of the one-pot sequential multiple arylation of imidazoles, oxazole and thiazole.

Initially, the C2, C4-sequential one-pot diarylation of C5-arylated *N*-methylimidazoles was carried out. The combination that showed the best overall yield in our previous stepwise synthesis of triarylated azoles (Scheme 1) was adopted for the one-pot sequential arylation of 5-(4-trifluoromethylphenyl)-*N*-

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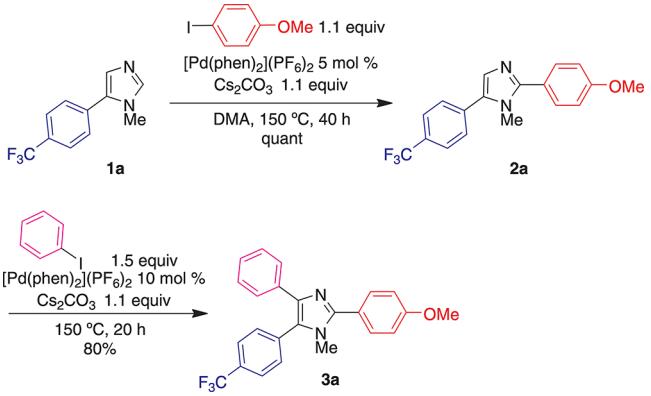
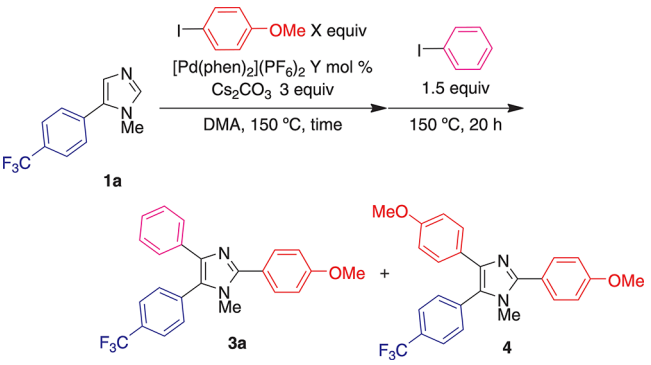
Scheme 1. Previous Example of the Stepwise Sequential Arylation of *N*-Methylimidazole



methylimidazole with *p*-methoxyphenyl iodide and phenyl iodide (Table 1).[7b] On the basis of the previous stepwise

Table 1. Optimization of the One-pot Sequential Arylation of *N*-Methylimidazole



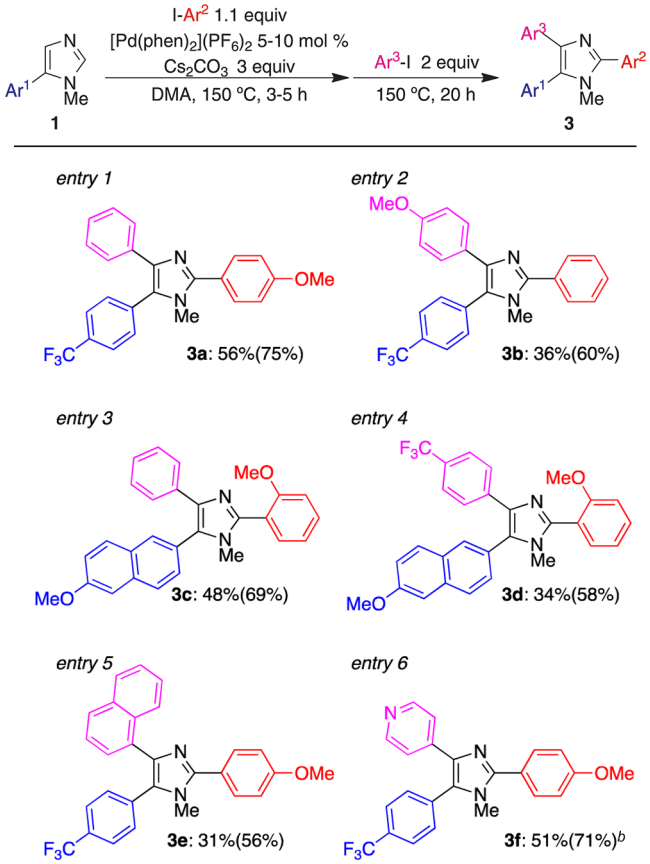
				yield (%)[a]	
entry	X (equiv)	Y (mol %)	time (h)	**3a**	**4**
1	1	15	3.5	48	19
2	1.1	5	3.5	56	14
3	1.3	5	4	47	30
4	1.5	5	4	38	53
5[b]	1.1	5	48	trace	13

[a]Isolated yields. [b]Monoarylated products containing PMP or phenyl at the C2 position were obtained in respective yields of 54 and 19%.

conditions, 15 mol % (total amount of the two steps) of $[Pd(phen)_2](PF_6)_2$ and 3 equiv (excess amount for the two reactions) of Cs_2CO_3 were initially used, and *p*-methoxyphenyl iodide (1 equiv) and phenyl iodide (1.5 equiv) were added sequentially to the reaction solution in this order. In the first arylation, **1** was consumed within 3.5 h as confirmed by GC analysis. After the first arylation was complete, phenyl iodide was added to the reaction solution, and the mixture was stirred for a further 20 h at that temperature to give the desired imidazole **3a** containing three different aryl groups, along with bismethoxyphenylated imidazole **4**, in respective yields of 48 and 19% (entry 1). Notably, **3a** could be readily isolated by conventional flash column chromatography on silica gel. The yield of **3a** improved with a lower catalyst loading (5 mol %) probably due to suppression of a competitive over-reaction (C2 and C4 diarylation) in the first step (entry 2). Even in this case, the yield of **4** significantly increased with a higher amount of *p*-methoxyphenyl iodide (entries 3 and 4). The catalyst was likely deactivated after 48 h in the first step, and the subsequent second arylation scarcely proceeded (entry 5).

With the results in hand, the scope of the one-pot diarylation was then investigated (Table 2).[11] Regioisomers **3a** and **3b**

Table 2. Examples of the One-pot Sequential Arylation of C5-Arylated *N*-Methylimidazoles[a]



[a]Isolated yields are indicated and formal average yields of the two steps are shown in parentheses. [b]The amount of Ar^2–I: 3 equiv.

were selectively obtained by simply changing the order of the addition of aryl iodides (entries 1 vs 2). Sterically hindered aryl groups such as 2-methoxyphenyl and 1-naphthyl groups were also allowed to couple at both the C2 and C4 positions under identical conditions in a selective manner (entries 3–5). In addition, a heteroaryl iodide, 4-pyridyl iodide, also coupled with the imidazole under the one-pot reaction conditions without a significant loss of efficiency (entry 6). It is noteworthy that those products were also easily isolated by flash column chromatography even if some byproducts formed.

This strategy could be applied to a substrate bearing a different substituent on the amino nitrogen of imidazole. For example, the one-pot sequential arylation of 5-phenyl-*N*-benzylimidazole (**5**) with *p*-methoxyphenyl iodide and trifluoromethylphenyl iodide gave the corresponding triarylated imidazole **6** in 41% overall yield, although a slightly higher catalyst loading was required (eq 2). In addition, the obtained **6** was readily debenzylated under conventional Pd/C-catalyzed hydrogenolysis conditions to give the imidazole **7** in quantitative yield (eq 3).

The one-pot sequential C2, C4-diarylation of oxazole and thiazole was then investigated (Table 3). The first C2-arylation

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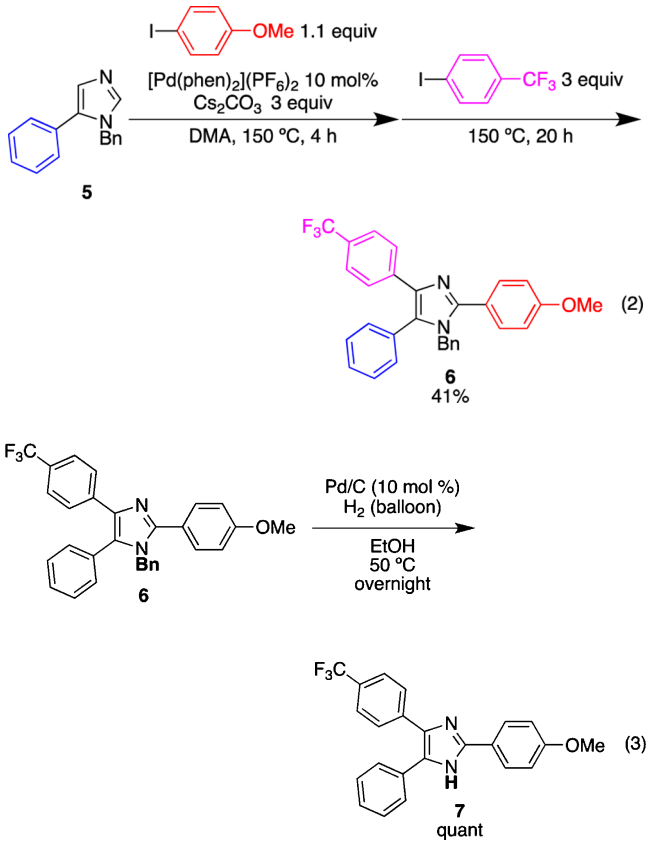
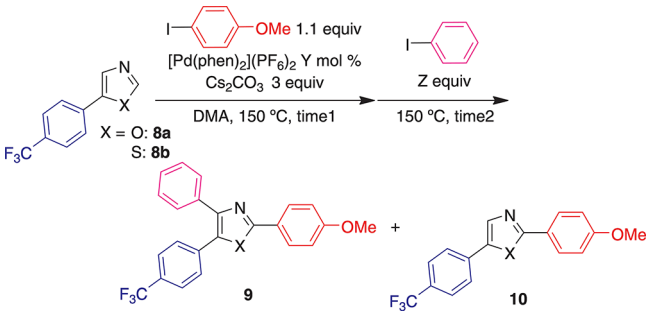


Table 3. One-pot Sequential Arylation of Oxazole and Thiazole



						yield (%)[a]	
entry	X	Y	Z	time1	time2	**9**	**10**
1	O	5	2	3	20	26	41
2	O	10	2	4	48	36	26
3	O	5	3	4	72	52	15
4	S	10	2	4	20	21	51
5	S	10	3	4	72	64	32

[a]Isolated yields.

of monoarylated azoles **8a** and **8b** with *p*-methoxyphenyl iodide was complete within 4 h regardless of the catalyst loading, as in the reaction of imidazoles. Meanwhile, longer reaction times were required for sufficient conversion in the second arylation in reactions of both substrates of azoles compared to that of *N*-methylimidazole. For example, the yield of triarylated **9a** improved to 52% when the reaction time of the second arylation was increased (entries 1−3). Similarly, the yield of **9b** reached 64% when the second reaction was carried out for 72 h (entry 5). Further prolongation of the reaction time did not affect the yield of products **9**, perhaps due to deactivation of the catalyst.

Finally, the one-pot triarylation of *N*-methylimidazole (**11**) was investigated. In the first step, due to the high activity of the catalyst $[Pd(phen)_2](PF_6)_2$, further competitive C2 arylation could not be avoided unless excess amount of *N*-methylimidazole was used as we reported.[7b] Therefore, the first monoarylation was carried out under Rossi's conditions.[12] Under these conditions, the substrate of *N*-methylimidazole was completely consumed after 4 h, as confirmed by GC analysis. As a first attempt, $[Pd(phen)_2](PF_6)_2$ (5 mol %), Cs_2CO_3 (3 equiv), and phenyl iodide (1.1 equiv) were added to the reaction mixture based on the conditions for the previous one-pot sequential diarylation (Table 2, entry 2). The resulting mixture was stirred for 4 h at 150 °C, and *p*-methoxyphenyl iodide (2 equiv) was then added to the reaction mixture. The resulting mixture was stirred for a further 20 h, but this did not lead to the formation of any of the desired product **3b** (Table 4, entry 1). Meanwhile, a small amount of **3b** was obtained by split additions of base in each step (total 2.5 equiv) and further addition of the catalyst in the final step (entry 2). Finally, the further portionwise addition of catalyst, halide, and base in the final step improved the yield of **3b** to 37% (average of each of the three steps: 72%) (entry 3). This result was comparable to the overall yield of **3b** from *N*-methylimidazole with the stepwise method (23−40%).[7b]

In conclusion, one-pot syntheses of triarylated azoles were developed based on $[Ph(phen)_2](PF_6)_2$-catalyzed sequential C−H bond arylation reactions. With these protocols, the resulting overall yields were comparable to those in the corresponding stepwise methods, and fewer chromatographic purification steps are necessary. Therefore, the one-pot protocols should be used as time- and cost-effective methods for the synthesis of triarylated azoles. Also, these protocols may be used as an attractive method for the high-throughput synthesis of triarylated azoles since the final products can be readily isolated by conventional chromatographic purification.

EXPERIMENTAL SECTION

General. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$. Chemical shifts of ^1H and ^{13}C are reported in δ values with reference to tetramethylsilane and $CDCl_3$ as internal standards, 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 (EI) in positive mode with a magnetic sector analyzer. All reactions were carried out in an argon atmosphere.

Materials. Unless otherwise noted, reagents were obtained commercially and used without purification. DMA was distilled over calcium hydride under reduced pressure. $[Pd(phen)_2](PF_6)_2$[13] and 5-(4-methoxy-6-naphth-2-yl)-*N*-methylimidazole (**1b**)[7b] were prepared as described in the literature. Silica gel 60N (Spherical, Neutral, 40−50 mm) from Kanto Chemical Co., Inc. was used for flash column chromatography.

General Procedure for the C5 Arylation of Azoles. DMA (0.5 M) was added to a screw-capped test tube and degassed by a freeze−pump−thaw cycle (3 times). To this was added $Pd(OAc)_2$ (5 mol %), tri(2-furyl)phosphine (10 mol %), K_2CO_3 (1 equiv), azoles, and aryl bromides (1 equiv). The resulting mixture was stirred overnight at 150 °C under an argon atmosphere. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel or by Kugelrohr distillation to give C5-arylated azoles **1a**, **5** and **8**.

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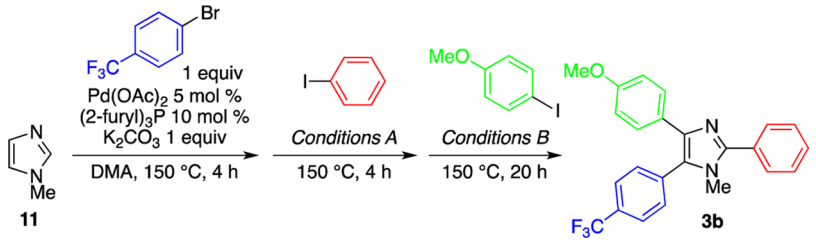
Table 4. One-pot Sequential Triarylation of *N*-Methylimidazole 8



entry	conditions A	conditions B	yield (%)[a]
1	Ph-I (1 equiv) $[Pd(phen)_2](PF_6)_2$ (5 mol %) Cs_2CO_3 (3 equiv)	PMP-I (2 equiv)	N.D.
2	Ph-I (1 equiv) $[Pd(phen)_2](PF_6)_2$ (5 mol %) **Cs_2CO_3 (1 equiv)**	PMP-I (1.5 equiv) **$[Pd(phen)_2](PF_6)_2$ (5 mol %) Cs_2CO_3 (1.5 equiv)**	7
3[b]	Ph-I (1 equiv) $[Pd(phen)_2](PF_6)_2$ (5 mol %) Cs_2CO_3 (1 equiv)	**PMP-I (3 equiv) $[Pd(phen)_2](PF_6)_2$ (15 mol %) Cs_2CO_3 (3 equiv)**	**37**

[a]Isolated yields. [b]In the final step, the catalyst, PMP-I, and Cs_2CO_3 were split into 6 portions, and the portions were added every 0.5 h.

***N*-Methyl-5-(4-trifluoromethylphenyl)imidazole (1a).**[7b] Colorless oil (154 mg, 68% yield), R_f = 0.10 (CH_2Cl_2/MeOH = 100:1). ^1H 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).

***N*-Benzyl-5-(4-trifluoromethylphenyl)imidazole (5).**[14] Yellow solid (112 mg, 48% yield), R_f = 0.25 (CH_2Cl_2/MeOH = 100:3). ^1H NMR ($CDCl_3$) δ 5.16 (s, 2H), 7.00–7.02 (m, 2H), 7.16 (s, 1H), 7.26–7.33 (m, 5H), 7.35–7.39 (m, 3H), 7.73 (s, 1H).

5-(4-Trifluoromethylphenyl)oxazole (8a).[15] Colorless solid (62 mg, 29% yield), R_f = 0.45 (hexane/EtOAc = 4:1). ^1H NMR ($CDCl_3$) δ 7.47 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.98 (s, 1H).

5-(4-Trifluoromethylphenyl)thiazole (8b).[16] Yellow solid (108 mg, 47% yield), R_f = 0.60 (hexane/EtOAc = 4:1). ^1H NMR ($CDCl_3$) δ 7.66 (d, J = 8.9 Hz, 2H), 7.69 (d, J = 8.9 Hz, 2H), 8.15 (s, 1H), 8.83 (s, 1H).

General Procedure for the One-pot Sequential Direct Diarylation of C5-Arylated Azoles (Tables 2 and 3, eq 2). DMA (0.5 M) was added to a screw-capped test tube and degassed by a freeze–pump–thaw cycle (3 times). To this was added $[Pd(phen)_2](PF_6)_2$ (5–10 mol %), Cs_2CO_3 (3 equiv), C5-arylated azoles (0.25 mmol), and aryl iodide (1.1 equiv). The reaction mixture was stirred for 3–5 h at 150 °C under an argon atmosphere and monitored by GC and TLC analysis. After the reaction was complete, the mixture was cooled to room temperature. To the resulting mixture was added another aryl iodide (2–3 equiv), and this was stirred for 20–72 h at 150 °C under an argon atmosphere. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the 2,4-diarylated products **3**, **6** and **9** and 2-monoarylated products **10**.

2-(4-Methoxyphenyl)-*N*-methyl-4-phenyl-5-(4-trifluoromethylphenyl)imidazole (3a)[7b] **(Table 1, entry 1).** Colorless solid (57 mg, 56% yield), R_f = 0.45 (hexane/EtOAc = 1:1). ^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).

4-(4-Methoxyphenyl)-*N*-methyl-2-phenyl-5-(4-trifluoromethylphenyl)imidazole (3b)[7b] **(Table 2, entry 2).** Yellow solid (37 mg, 36% yield), R_f = 0.45 (hexane/EtOAc = 1:1). ^1H NMR ($CDCl_3$) δ 3.53 (s, 3H), 3.79 (s, 3H), 6.79 (d, J = 8.9 Hz, 2H), 7.45–7.48 (m, 5H), 7.50 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.83 (br, 2H).

5-(6-Methoxynaphth-2-yl)-2-(2-methoxyphenyl)-*N*-methyl-4-phenylimidazole (3c) (Table 2, entry 3). Yellow solid (51 mg, 48% yield), mp 87–88 °C, R_f = 0.15 (hexane/EtOAc = 4:1), IR (KBr) 2933, 1606, 1496, 1469, 1387, 1251, 1023, 909, 759, 726, 697 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 7.02 (d, J = 8.5 Hz, 1H), 7.10–7.22 (m, 6H), 7.46–7.50 (m, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.67 (d, J = 7.1 Hz, 1H), 7.77 (d, J = 9.4 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.87 (s, 1H). ^{13}C NMR ($CDCl_3$) 32.4, 55.5, 55.7, 105.8, 111.0, 121.1, 126.3, 126.4, 126.7, 127.0, 127.4, 127.6, 128.1, 128.3, 128.5, 128.6, 128.8, 129.1, 129.8, 129.9, 131.1, 132.8, 134.4, 145.6, 157.6, 158.4. MS (EI) m/z 420 (M^+). HRMS (EI): Calcd for $C_{28}H_{24}N_2O_2$ (M^+) 420.1838, Found 420.1841.

5-(6-Methoxynaphth-2-yl)-2-(2-methoxyphenyl)-*N*-methyl-4-(4-trifluoromethylphenyl)imidazole (3d) (Table 2, entry 4). Yellow solid (42 mg, 34% yield), mp 88–89 °C, R_f = 0.68 (hexane/EtOAc = 1:1). IR (KBr) 2924, 1617, 1493, 1325, 1251, 1165, 1122, 1064 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.34 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 7.03 (d, J = 8.1 Hz, 2H), 7.11–7.15 (m, 1H), 7.21–7.23 (m, 3H), 7.38–7.44 (m, 3H), 7.66–7.71 (m, 2H), 7.76 (d, J = 9.4 Hz, 1H), 7.85 (d, J = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 32.4, 55.5, 55.7, 105.9, 111.1, 114.3, 119.7, 121.2, 124.1 (q, J = 271.5 Hz), 125.1 (q, J = 3.8 Hz), 125.7, 126.8, 127.9, 127.9 (q, J = 32.0 Hz), 128.6, 129.0, 129.8, 130.0, 131.1, 131.4, 132.8, 134.6, 135.9, 138.0, 146.0, 157.6, 158.7. ^{19}F NMR ($CDCl_3$) δ −58.7. MS (EI) m/z 488 (M^+). HRMS (EI): Calcd for $C_{29}H_{23}F_3N_2O_2$ (M^+) 488.1712, Found 488.1707.

2-(4-Methoxyphenyl)-*N*-methyl-4-(naphth-1-yl)-5-(4-trifluoromethylphenyl)imidazole (3e) (Table 2, entry 5). Colorless solid (35 mg, 31% yield), mp 93–94 °C, R_f = 0.18 (hexane/EtOAc = 1:4). IR (KBr) 2936, 2360, 1613, 1455, 1323, 1252, 1168, 1122 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.87 (s, 3H), 7.03 (d, J = 8.5 Hz, 2H), 7.30–7.33 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.41–7.45 (m, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.76–7.78 (m, 3H), 7.81–7.84 (dd, J = 6.8 Hz, 1.8 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 34.2, 55.5, 114.1, 124.1 (q, J = 272.1 Hz), 123.0, 125.3, 125.6 (q, J = 3.8 Hz), 125.7, 126.0, 126.6, 128.1, 128.2, 128.6, 129.5 (q, J = 32.3 Hz), 130.2, 130.6, 130.9, 132.0, 132.6, 134.0, 134.3, 139.0, 149.0, 160.3. ^{19}F NMR ($CDCl_3$) δ −59.0. MS (EI) m/z 458 (M^+). HRMS (EI): Calcd for $C_{28}H_{21}F_3N_2O$ (M^+) 458.1606, Found 458.1602.

2-(4-Methoxyphenyl)-*N*-methyl-4-pyridyl-5-(4-trifluoromethylphenyl)imidazole (3f) (Table 2, entry 6). Yellow solid (52 mg, 51% yield), mp 178–179 °C, R_f = 0.10 (hexane/EtOAc = 1:2), IR (KBr) 2923, 1600, 1332, 1255, 1121, 1072, 830 cm^{-1}. ^1H NMR ($CDCl_3$) 3.48 (s, 3H), 3.87 (s, 3H), 7.03 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 6.3 Hz, 2H), 7.55 (d, 8.1 Hz, 2H), 7.64 (d, 8.6 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 8.42 (d, 6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) 33.3, 55.4, 114.2, 121.1, 122.2, 123.8 (q, J = 271.8 Hz), 126.4 (q, J = 3.3 Hz), 130.4, 130.7, 131.4 (q, J = 33.0 Hz), 131.6, 134.0, 134.9, 143.3, 148.0, 149.4, 160.5. ^{19}F NMR ($CDCl_3$) −59.1. MS (EI) m/z 409 (M^+). HRMS(EI): Calcd for $C_{23}H_{18}F_3N_3O$ (M^+) 409.1402, Found 409.1401.

***N*-Benzyl-2-(4-methoxyphenyl)-4-(4-trifluoromethylphenyl)-5-phenylimidazole (6) (eq 2).** Colorless solid (50 mg, 41% yield), mp 134–136 °C, R_f = 0.18 (hexane/EtOAc = 4:1), IR (KBr) 2930, 1616, 1577, 1251, 1162, 1120, 1065 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 5.09 (s, 2H), 6.79–6.82 (m, 2H), 6.93 (d, J = 8.8 Hz, 2H) 7.18–7.23 (m, 5H), 7.32–7.41 (m, 3H) 7. 44 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.66 (d J = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 48.2, 55.3, 114.1, 122.9, 124.4 (q, J = 271.8 Hz), 125.0 (q, J = 4.1 Hz), 125.9, 126.5, 127.4, 127.9 (q, J = 32.2 Hz), 128.6, 128.9, 129.0, 130.4, 130.6, 130.9, 131.0, 136.4, 137.3, 138.0, 148.3, 160.2. ^{19}F NMR

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($CDCl_3$) δ −58.7. HRMS (EI): m/z 484 (M^+) Calcd for $C_{30}H_{23}F_3N_2O$ (M^+) 484.1762, Found 484.1766.

2-(4-Methoxyphenyl)-4-phenyl-5-(4-trifluoromethylphenyl)-oxazole (9a) (Table 3, entry 3). Colorless solid (51 mg, 52% yield), mp 130−131 °C, R_f = 0.18 (hexane/EtOAc = 1:4). IR (KBr) 2360, 1615, 1500, 1326, 1257, 1169, 839 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.00 (d, J = 8.9 Hz, 2H), 7.39−7.45 (m, 3H), 7.60 (d, J = 8.1 Hz, 2H), 7.67−7.69 (m, 2H), 7.75 (d, J = 8.1 Hz, 2H), 8.10 (d, J = 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.4, 114.2, 119.6, 125.3 (q, J = 271.8 Hz), 125.6 (q, J = 4.1 Hz), 126.1, 128.3, 128.3, 128.7, 128.8, 129.8 (q, J = 32.3 Hz), 132.2, 132.4, 138.4, 143.4, 160.9, 161.6. ^{19}F NMR ($CDCl_3$) δ −63.1. MS (EI) m/z 395 (M^+). HRMS (EI): Calcd for $C_{23}H_{16}F_3NO_2$ (M^+) 395.1133, Found 395.1123.

2-(4-Methoxyphenyl)-5-(4-trifluoromethylphenyl)oxazole (10a)[17] (Table 3, entry 3). Colorless solid (12 mg, 15% yield), R_f = 0.11 (hexane/EtOAc = 20:1). ^1H NMR ($CDCl_3$) 3.88 (s, 3H), 7.00 (d, J = 9.0 Hz, 2H), 7.51 (s, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H), 8.07 (d, J = 9.0 Hz, 2H).

2-(4-Methoxyphenyl)-4-phenyl-5-(4-trifluoromethylphenyl)-thiazole (9b) (Table 3, entry 5). Yellow solid (66 mg, 64% yield), mp 105−107 °C, R_f = 0.63 (hexane/EtOAc = 4:1). IR (KBr) 1605, 1326, 1257, 1169, 1119, 1070, 826, 699 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 6.97 (d, J = 8.8 Hz, 2H), 7.33−7.35 (m, 3H), 7.49 (d, J = 8.3 Hz, 2H), 7.55−7.57 (m, 4H), 7.96 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.4, 114.3, 124.0 (q, J = 271.8 Hz), 125.7 (q, J = 4.1 Hz), 126.3, 128.0, 128.2, 128.5, 129.2, 129.7, 129.8 (q, J = 32.2 Hz), 130.1, 134.6, 136.0, 151.7, 161.4, 166.3. ^{19}F NMR ($CDCl_3$) δ −59.0. MS (EI) m/z 411 (M^+). HRMS (EI): Calcd for $C_{23}H_{16}F_3NOS$ (M^+) 411.0905, Found 411.0890.

2-(4-Methoxyphenyl)-5-(4-trifluoromethylphenyl)thiazole (10b) (Table 3, entry 5). Orange solid (27 mg, 32% yield), mp 160−162 °C, R_f = 0.63 (hexane/EtOAc = 4:1). IR (KBr) 1603, 1438, 1330, 1262, 1173, 1123, 1071, 832 cm^{-1}. ^1H NMR ($CDCl_3$) 3.87 (s, 3H), 6.98 (d, J = 8.9 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.9 Hz, 2H), 8.13 (s, 1H). ^{13}C NMR ($CDCl_3$) 55.6, 124.0 (q, J = 271.5 Hz), 125.8, 126.2 (q, J = 3.8 Hz), 126.7, 127.1, 128.3, 130.1 (q, J = 33.8 Hz), 134.9, 136.6, 139.5, 161.8, 168.6, ^{19}F NMR ($CDCl_3$) −50.4. MS (EI) m/z 335 (M^+). HRMS (EI): Calcd for $C_{17}H_{12}F_3NOS$ (M^+) 335.0592, Found 335.0591.

Debenzylation of *N*-Benzyl-2-(4-methoxyphenyl)-4-(4-trifluoromethylphenyl)-5-phenyl-imidazole (6) Leading to 2-(4-Methoxyphenyl)-5-phenyl-4-(4-trifluoromethylphenyl)-1*H*-imidazole 7 (eq 3). To a solution of 1-benzyl-2-(4-methoxyphenyl)-4-(4-trifluoromethylphenyl)-5-phenylimidazole (**6**) (0.15 mmol) in EtOH (1 mL) was added Pd/C (10 mol %). The suspension was stirred overnight at 50 °C under a H_2 atmosphere. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to give 2-(4-methoxyphenyl)-5-phenyl-4-(4-trifluoromethylphenyl)-1*H*-imidazole **7** in quantitative yield (59 mg). Yellow solid, mp 187−188 °C, R_f = 0.25 (hexane/EtOAc = 4:1), IR (KBr) 1614, 1469, 1410, 1250, 1163, 1118, 1065, 1021, 849 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 6.96 (d, J = 8.5 Hz, 2H), 7.35−7.40 (m, 3H), 7.48 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 7.88 (d, J = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.4, 114.4, 120.7, 124.2 (q, J = 271.5 Hz), 125.3 (q, J = 3.7 Hz), 127.8, 128.0, 128.3, 128.5, 128.9, 129.3 (q, J = 32.8 Hz), 129.8, 130.4, 132.4, 135.7, 146.3, 161.0. ^{19}F NMR ($CDCl_3$) δ −62.8. MS (EI) m/z 394 (M^+). HRMS (EI): Calcd for $C_{23}H_{17}F_3N_2O$ (M^+) 394.1293, Found 394.1292.

The One-pot Sequential Direct Triarylation of *N*-Methylimidazole (Table 4, entry 3). DMA (0.5 M) was added to a screw-capped test tube and degassed by a freeze−pump−thaw cycle (3 times). To this was added $Pd(OAc)_2$ (5 mol %), tri(2-furyl)phosphine (10 mol %), K_2CO_3 (1 equiv), *N*-methylimidazole (1 mmol), and 4-bromobenzotrifluoride (1 equiv). The mixture was stirred for 4 h at 150 °C under an argon atmosphere. The reaction mixture was then cooled to room temperature. To this was added iodobenzene (1 equiv), Cs_2CO_3 (1 equiv), and $[Pd(phen)_2](PF_6)_2$ (5 mol %), and the mixture was stirred for 4 h at 150 °C under an argon atmosphere. Subsequently, 4-iodoanisole (3 equiv), Cs_2CO_3 (3 equiv), and $[Pd(phen)_2](PF_6)_2$ (15 mol %) were split into 6 portions, respectively, and added portionwise to the reaction mixture every 0.5 h at 150 °C. The resulting mixture was stirred at that temperature for 20 h under an argon atmosphere. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to give *N*-methyl-4-(4-methoxyphenyl)-2-phenyl-5-(4-trifluoromethylphenyl)-imidazole (**3b**) in 37% yield (151 mg).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR for novel compounds and ^1H NMR for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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