Efficient C-7 or C-3/C-7 Direct Arylation of Tri- or Disubstituted Imidazo-[1,2-*b*]pyrazoles

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Abstract: A novel and efficient method of C-7 direct arylation of the imidazo[1,2-*b*]pyrazole core, never described to date, is presented in this paper. Series of electron-rich or electron-poor aryl and heteroaryl groups were easily introduced. The corresponding products were obtained in moderate to excellent yields thanks to this pallado-catalyzed and microwave-assisted process. A one-pot double C-3 and C-7 direct coupling is also reported.

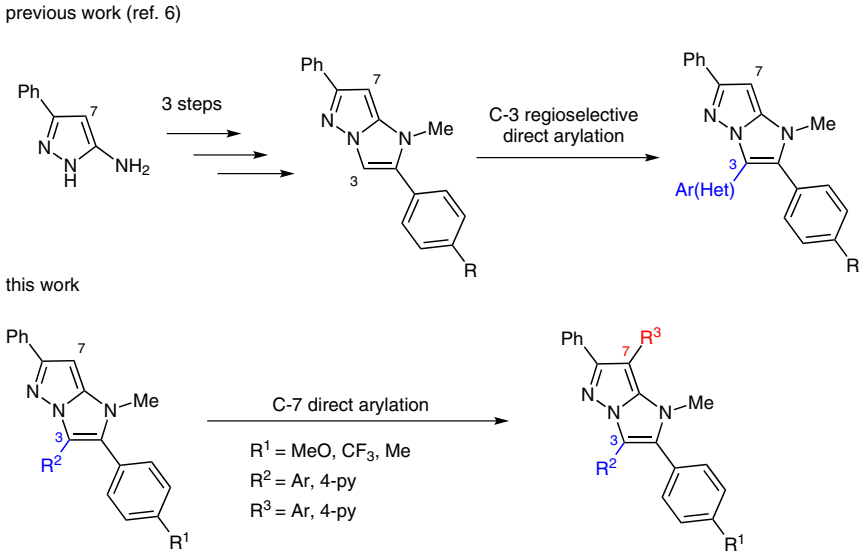
Key words: C–C coupling, arylation, fused-ring systems, microwave chemistry, palladium

In recent years, polycyclic scaffolds containing heteroatoms such as nitrogens have attracted much attention in the field of drug discovery. More precisely, imidazo[1,2-*b*]pyrazole derivatives have been designed, prepared and studied as anticancer,[1] antifungal[2] and anti-inflammatory agents.[3] They can also play an important role in the treatment of neurodegenerative disorders.[4]

The synthesis of the imidazo[1,2-*b*]pyrazole skeleton, therefore, provides an interesting challenge. Current synthetic methods of such compounds generally consist in constructing the 5-5 fused ring system with the desired substituents in appropriate positions.[1a,b,2b,5] Strategies of direct functionalization of the heterobicyclic moiety have rarely been reported. Developing new synthetic and functionalization strategies therefore continues to be essential in generating diversified libraries of potentially bioactive molecules.

At the beginning of our research in this field, we developed an original synthesis of the imidazo[1,2-*b*]pyrazole core through a three-step route. We then reported the first regioselective C-3 direct arylation of the imidazo[1,2-*b*]pyrazole system.[6] The methodology allows rapid access to a wide range of trisubstituted imidazo[1,2-*b*]pyrazole compounds. To pursue our objectives,[7] we now envision studying the reactivity of carbon C-7 toward direct C–H arylation (Scheme 1).

The direct C–H arylation of aromatic and heteroaromatic compounds has been successfully accomplished in recent years. Such cross-couplings are very attractive compared to more classical palladium-catalyzed reactions such as Suzuki, Stille and Negishi coupling as they do not require



Scheme 1 Previous versus current work

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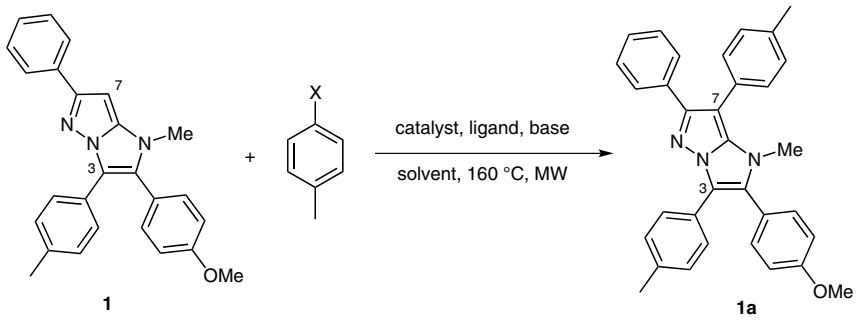


Scheme 2 Screening of the palladium-catalyzed direct C-7 arylation conditions

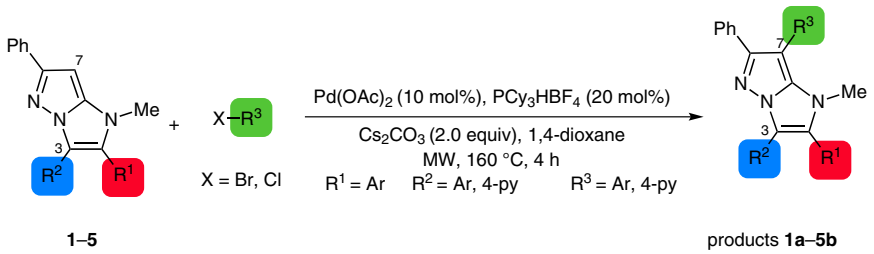
the preliminary preparation of organometallic reagents.[8] Noticeably, arylation of electron-poor heterocycles such as five-membered heterocycles bearing two or three heteroatoms, is a compelling challenge in this field today.[9] To the best of our knowledge, this work constitutes the first successful palladium-catalyzed direct C-7 functionalization of the imidazo[1,2-*b*]pyrazole core.

Our study was initiated by working on 2-(4-methoxyphenyl)-1-methyl-6-phenyl-3-(*p*-tolyl)-1*H*-imidazo[1,2-*b*]-pyrazole (**1**, Scheme 2). This starting material was easily synthesized in a four-step process from the commercially available 3(5)-phenyl-1*H*-pyrazol-5(3)-amine.[6] We first applied the conditions optimized for C-3 direct arylation, namely palladium acetate (10 mol%), tricyclohexylphosphine (20 mol%), potassium carbonate (2.0 equiv).[6] However, two equivalents of 4-bromotoluene were used. These conditions led to a poor conversion of 27% (Table 1, entry 1). The conversion was based on the ratio of NMR integrations of the NMe signal from the product and the starting material. Using a stronger base such as cesium carbonate enhanced the conversion to 47% (Table 1, entry 2), whereas the use of a non-carbonate base such as potassium acetate was unsuccessful (Table 1, entry 3). Adding pivalic acid[10] as additive did not improve the conversion

Table 1 Screening of the Palladium-Catalyzed Direct C-7 Arylation Conditions[a]

Entry	Catalyst (mol%)	Ligand (mol%)	Base (2.0 equiv)	X (equiv)	Solvent	Time (h)	Conversion (%)[b] [Yield (%)][c]
1	$Pd(OAc)_2$ (10)	PCy_3 (20)	K_2CO_3	Br (2.0)	1,4-dioxane	1	27
2	$Pd(OAc)_2$ (10)	PCy_3 (20)	Cs_2CO_3	Br (2.0)	1,4-dioxane	1	47
3	$Pd(OAc)_2$ (10)	PCy_3 (20)	KOAc	Br (2.0)	1,4-dioxane	1	24
4	$Pd(OAc)_2$ (10)	PCy_3 (20)	Cs_2CO_3	Br (2.0)	1,4-dioxane	1	42[d]
5	$Pd(OAc)_2$ (10)	*t*-Bu_3PHBF_4 (20)	Cs_2CO_3	Br (2.0)	1,4-dioxane	1	32
6	$Pd(OAc)_2$ (10)	PCy_3HBF_4 (20)	Cs_2CO_3	Br (2.0)	1,4-dioxane	1	69
7	$Pd(OAc)_2$ (10)	PCy_3HBF_4 (20)	Cs_2CO_3	Br (2.0)	toluene	1	58
8	$Pd(OAc)_2$ (10)	PCy_3HBF_4 (20)	Cs_2CO_3	Br (2.0)	DMA	1	52
9	$Pd(OAc)_2$ (10)	PCy_3HBF_4 (20)	Cs_2CO_3	Br (4.0)	1,4-dioxane	1	67
10	$Pd(OAc)_2$ (15)	PCy_3HBF_4 (30)	Cs_2CO_3	Br (2.0)	1,4-dioxane	1	72
11	$Pd(OAc)_2$ (10)	PCy_3HBF_4 (20)	Cs_2CO_3	Br (2.0)	1,4-dioxane	2	84
12	$Pd(OAc)_2$ (10)	PCy_3HBF_4 (20)	Cs_2CO_3	Br (2.0)	1,4-dioxane	3	92
13	**$Pd(OAc)_2$ (10)**	**PCy_3HBF_4 (20)**	**Cs_2CO_3**	**Br (2.0)**	**1,4-dioxane**	**4**	**100 (95)**
14	$Pd(OAc)_2$ (5)	PCy_3HBF_4 (10)	Cs_2CO_3	Br (2.0)	1,4-dioxane	4	70
15	$Pd(OAc)_2$ (10)	PCy_3HBF_4 (20)	Cs_2CO_3	Cl (2.0)	1,4-dioxane	4	100 (89)
16	$Pd(OAc)_2$ (10)	PCy_3HBF_4 (20)	Cs_2CO_3	I (2.0)	1,4-dioxane	4	10

[a] The reactions were carried out with **1** (0.254 mmol), 4-halogenotoluene (specified quantities), palladium acetate (specified quantities), ligand (specified quantities), and base (2.0 equiv) in solvent (2 mL).
[b] ^1H NMR ratio based on the integration of NMe.
[c] Isolated yields after column chromatography.
[d] Pivalic acid (20 mol%) was added.



Scheme 3 Synthesis of products **1a**–**5b**

(Table 1, entry 4). Furthermore, a rapid survey of different ligands showed that tricyclohexylphosphine tetrafluoroborate was the best candidate because a 69% conversion was achieved (Table 1, entry 6). Switching the solvent system to toluene or a more polar solvent such as dimethylacetamide was not beneficial (Table 1, entries 7 and 8). Increasing the amount of aryl bromide to four equivalents did not improve the reaction outcome (Table 1, entry 9). Moreover, the increment in the catalyst loading induced no noticeable change (Table 1, entry 10). However, increasing the time of the reaction gradually improved the conversion (Table 1, entries 11 and 12). We were pleased to observe that the starting material was completely consumed after four hours heating and the expected product was isolated in an excellent yield of 95% (Table 1, entry 13). Decreasing the catalyst loading to 5 mol% of $Pd(OAc)_2$ and 10 mol% of PCy_3 did not maintain the coupling efficiency (Table 1, entry 14). The reaction was also performed using the corresponding 4-chlorotoluene as coupling partner. A slightly lower yield was achieved (Table 1, entry 15). The extension of our methodology to aryl chlorides is a powerful result as these substrates are generally less expensive and more readily available than their bromo or iodo analogues.[11] This suggests the possibility of introducing a larger range of functional groups. However, using the 4-iodotoluene only led to a low conversion of 10% (Table 1, entry 16). To sum up, the best conditions were found to be palladium acetate (10 mol%), tricyclohexylphosphine tetrafluoroborate (20 mol%), 4-bromo- or 4-chlorotoluene (2.0 equiv) and cesium carbonate (2.0 equiv) in 1,4-dioxane at 160 °C under microwave irradiation during four hours.

To probe the scope of the reaction, the use of different imidazo[1,2-*b*]pyrazole synthons and various aryl or heteroaryl bromides was examined (Scheme 3). The expected products were cleanly obtained in good to excellent yields using *para* electron-withdrawing groups such as CF_3 or CN or soft electron-donating groups such as methyl onto aryl bromide (Table 2, entries 1, 2, 4, 5, 8, 9 and 13–16). For unknown reasons, the presence of a methoxy group affected the efficiency of the reaction because a partial conversion was noted (Table 2, entry 3). The increase in the time of the reaction or the amount of coupling partner did not produce any improvement. The same behavior was observed with 4-bromopyridine. Compounds with a pyridinyl group in C-7 (**1d**, **2c**, **3c**) were obtained in 41–71% yield (Table 2, entries 4, 7 and 10). The starting material was easily separated from the product and recycled. Fortunately, the efficiency of our methodology was maintained using *ortho*- or *meta*-substituted aryl bromides (Table 2, entries 11 and 12). The compounds **3d** and **3e** were isolated in good yields of 78% and 71%, respectively.

Comparable yields were reached using various (hetero)aryl chlorides (Table 2, entries 1–4). This result highlights the great versatility of our strategy.

Table 2 Scope of the Pd-Catalyzed C-7 Direct Arylation of **1**–**5**

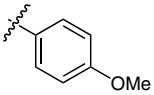
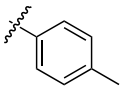
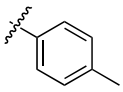
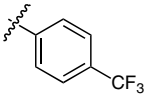
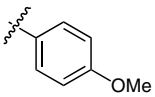
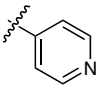
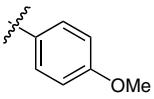
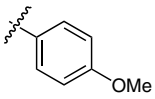
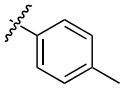
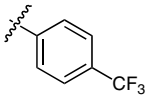
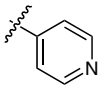
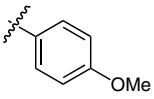
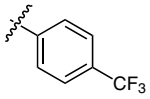
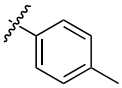
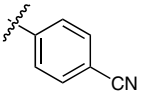
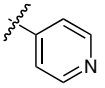
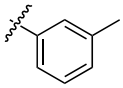
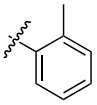
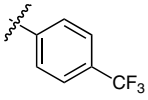
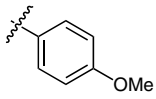
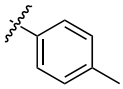
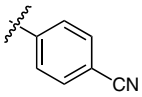
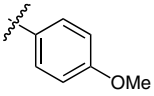
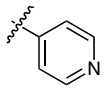
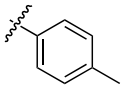
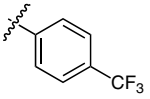
Entry	Starting material	R^1	R^2	R^3	Product	Yield (%)[a]
1	**1**				**1a**	95 (89)[b]
2					**1b**	90 (87)[b]
3					**1c**	64[c] (68)[b,d]
4					**1d**	41[e] (39)[b,f]

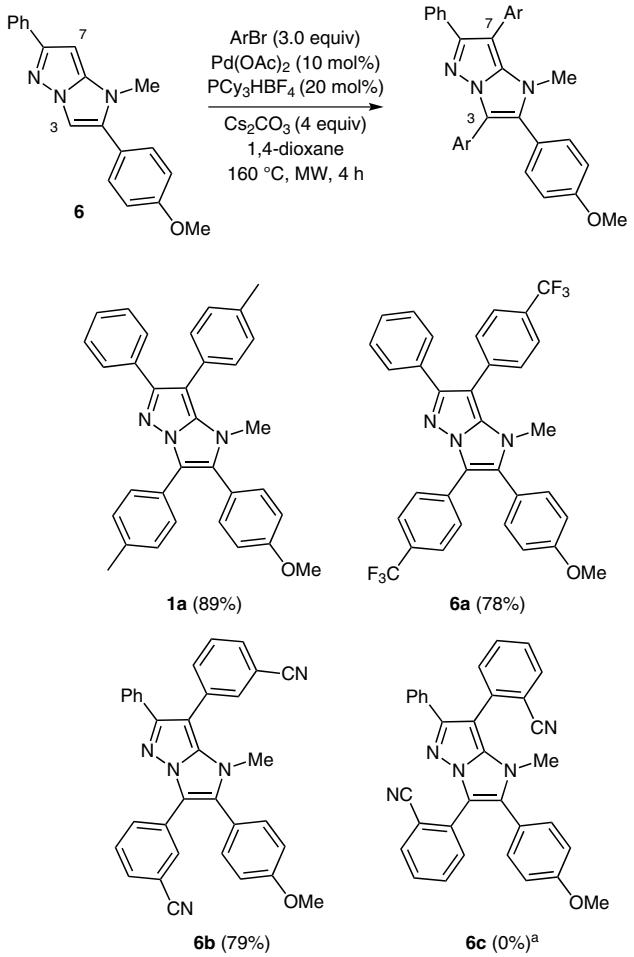
Table 2 Scope of the Pd-Catalyzed C-7 Direct Arylation of **1**–**5** (continued)

Entry	Starting material	R^1	R^2	R^3	Product	Yield (%)[a]
5	**2**				**2a**	86
6					**2b**	86
7					**2c**	70[g]
8	**3**				**3a**	91
9					**3b**	82
10					**3c**	66[h]
11					**3d**	78
12					**3e**	71
13	**4**				**4a**	71
14					**4b**	74
15	**5**				**5a**	72
16					**5b**	74

[a] Isolated yields after column chromatography.
[b] The reaction was performed using the 4-chloro analogue as coupling partner.
[c] Amount of starting material recovered was 28%.
[d] Amount of starting material recovered was 25%.
[e] Amount of starting material recovered was 49%.
[f] Amount of starting material recovered was 45%.
[g] Amount of starting material recovered was 23%.
[h] Amount of starting material recovered was 25%.

Remarkably, the optimized palladium-catalyzed process was successfully applied to a large variety of imidazo[1,2-*b*]pyrazoles bearing different groups in C-2 and C-3 positions. Indeed, we were pleased to notice that aryl-bearing electron-rich (MeO, Me) or electron-poor (CF_3) substituents or heterocycles such as pyridine in C-2 or C-3 position are well tolerated.

As the last part of this work, we also extended the methodology to a double and one-pot C-3 and C-7 direct arylation of the disubstituted imidazo[1,2-*b*]pyrazole **6** prepared according to the strategy previously described by our group.[6] The amounts of aryl bromide and base were increased to three and four equivalents, respectively (see Scheme 4). Gratifyingly, the strategy proved to be highly effective because 3,7-bis(4-trifluoromethyl)phenyl and 3,7-bis(4-tolyl)imidazo[1,2-*b*]pyrazole derivatives were obtained in 78% and 89% yields, respectively. The C–C coupling was also accomplished with aryl bromides bearing *meta* and *ortho* substituents. Interestingly, the *meta*-benzonitrile group was successfully introduced. Unfortunately, in the case of the *ortho*-substituted cyano compound, only the mono C-3 arylated product was isolated.



Scheme 4 One-pot C-3 and C-7 direct arylation. [a] Only the C-3 mono-arylated compound was obtained (64%).

Several mechanistic scenarios have been proposed to explain palladium-catalyzed direct arylation outcomes including S_EAr, Heck-like addition, CMD (concerted metalation–deprotonation) and nCMD (non-concerted metalation–deprotonation) mechanism.[12]

The set of experiment achieved here is insufficient to explain the mechanism involved in this direct C–H arylation. In fact, the non-improvement of the reactivity in presence of pivalate or potassium acetate[13] and the low conversion observed when the aryl iodide[14] is used may not discard the carbonate-assisted metalation–deprotonation mechanism (CMD). Further studies (DFT calculations, kinetic isotopic effect, etc.) are necessary to draw more precise conclusions.

In conclusion, we have disclosed herein the first strategy for C-7 direct arylation of C-3-substituted imidazo[1,2-*b*]pyrazoles.[15] The method enables the synthesis of a large variety of tetra(hetero)arylated imidazopyrazole derivatives. Moderate to excellent yields were achieved from readily available electron-poor or electron-rich aryl or heteroaryl bromides or chlorides.

Acknowledgment

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References and Notes

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(15) **General Procedure A; C-7 Direct Arylation of the Imidazo[1,2-*b*]pyrazoles 1–5**: A microwave vial containing a stirring bar was loaded with imidazo[1,2-*b*]pyrazole **1**–**5** in 1,4-dioxane, (hetero)aryl bromide or chloride (2.0 equiv), tricyclohexylphosphine tetrafluoroborate (0.20 equiv) and cesium carbonate (2.0 equiv). The tube was evacuated and backfilled with dry argon twice. Palladium acetate (0.10 equiv) was added and the mixture was submitted to microwave irradiation with stirring at 160 °C for 4 h. It was then cooled to r.t., and 1,4-dioxane was removed under reduced pressure. The residue was purified by flash chromatography to provide the desired products **1a**–**5b**.

2-(4-Methoxyphenyl)-1-methyl-6-phenyl-3-(4-tolyl)-7-[4-(trifluoromethyl)phenyl]-1*H*-imidazo[1,2-*b*]pyrazole (1b): The reaction was carried out as described in general procedure A using imidazo[1,2-*b*]pyrazole **1** (100 mg, 0.254 mmol), palladium acetate (5.7 mg, 0.0254 mmol), tricyclohexylphosphine tetrafluoroborate (18.7 mg, 0.0508 mmol), cesium carbonate (142 mg, 0.508 mmol) and 4-bromobenzotrifluoride (114 mg, 72 μL, 0.508 mmol) in 1,4-dioxane (2 mL). Standard workup followed by flash chromatography (CH_2Cl_2–petroleum ether, 1:1) yielded **1b** as a pale yellow solid (123 mg, 90%); mp 226–228 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.1 Hz, 2 H, H_{Ar}), 7.58 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.53 (d, *J* = 7.9 Hz, 2 H, H_{Ar}), 7.47 (d, *J* = 8.1 Hz, 2 H, H_{Ar}), 7.33 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.25–7.29 (m, 3 H, H_{Ar}), 7.12 (d, *J* = 8.1 Hz, 2 H, H_{Ar}), 7.00 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 3.88 (s, 3 H, OMe), 3.30 (s, 3 H, NMe), 2.32 (s, 3 H, Me). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.31 (C_q), 152.26 (C_q), 140.07 (C_q), 137.17 (C_q), 136.82 (C_q), 134.27 (C_q), 132.46 (CH_{Ar}), 130.97 (CH_{Ar}), 129.19 (C_q), 129.03 (CH_{Ar}), 128.87 (CH_{Ar}), 128.18 (CH_{Ar}), 127.87 ($^2J_{C–F}$ = 33.0 Hz, C_q), 127.42 (CH_{Ar}), 127.14 (CH_{Ar}), 125.63 (C_q), 125.14 ($^3J_{C–F}$ = 3.72 Hz, CH_{Ar}), 124.41 ($^1J_{C–F}$ = 273 Hz, C_q), 121.13 (C_q), 118.42 (C_q), 114.64 (CH_{Ar}), 94.33 (C_q), 55.34 (OMe), 31.73 (NMe), 21.29 (Me). IR (neat): 1603, 1322, 1118, 1066, 838, 697 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{27}F_3N_3O$: 538.21007; found: 538.21007. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{27}F_3N_3O$: 560.19202; found: 560.19113.

General Procedure B; One-Pot C-3 and C-7 Direct Arylation of Imidazo[1,2-*b*]pyrazole 6: A microwave vial containing a stirring bar was loaded with imidazo[1,2-*b*]pyrazole **6** in 1,4-dioxane, (hetero)aryl bromide (3.0 equiv), tricyclohexylphosphine tetrafluoroborate (0.20 equiv) and cesium carbonate (4.0 equiv). The tube was evacuated and back-filled with dry argon twice. Palladium acetate (0.10 equiv) was added and the mixture was submitted to microwave irradiation with stirring at 160 °C for 4 h. It was then cooled to r.t., and 1,4-dioxane was removed under reduced pressure. The residue was purified by flash chromatography to provide the desired products **1a**, **6a** and **6b**.

2-(4-Methoxyphenyl)-1-methyl-6-phenyl-3,7-bis[4-(trifluoromethyl)phenyl]-1*H*-imidazo[1,2-*b*]pyrazole (6a): The reaction was carried out as described in general procedure B using imidazo[1,2-*b*]pyrazole **6** (100 mg, 0.329 mmol), palladium acetate (8.04 mg, 0.0329 mmol), tricyclohexylphosphine tetrafluoroborate (24.0 mg, 0.0658 mmol), caesium carbonate (369 mg, 1.32 mmol) and 4-bromobenzotrifluoride (222 mg, 138 μL, 0.987 mmol) in

1,4-dioxane (2 mL). Standard workup followed by flash chromatography (CH_2Cl_2–petroleum ether, 3:7) yielded **6a** as a white solid (151 mg, 78%); mp 220–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.47–7.64 (m, 8 H, H_{Ar}), 7.29–7.41 (m, 5 H, H_{Ar}), 7.07 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 3.92 (s, 3 H, OMe), 3.33 (s, 3 H, NCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.76 (C_q), 152.49 (C_q), 140.08 (C_q), 136.81 (C_q), 133.96 (C_q), 132.34 (CH_{Ar}), 132.28 (C_q), 131.09 (C_q), 131.05 (CH_{Ar}), 128.78 (CH_{Ar}), 128.37 ($^2J_{C–F}$ = 32.6 Hz, C_q), 128.27 (CH_{Ar}), 128.20 ($^2J_{C–F}$ = 32.8 Hz, C_q), 127.64 (CH_{Ar}), 126.73 (CH_{Ar}), 125.25 ($^3J_{C–F}$ = 3.70 Hz, 2 × CH_{Ar}), 124.36 ($^1J_{C–F}$ = 273 Hz, C_q), 124.18 ($^1J_{C–F}$ = 273 Hz, C_q), 120.39 (C_q), 117.03 (C_q), 114.99 (CH_{Ar}), 94.65 (C_q), 55.39 (OMe), 31.74 (NMe). IR (neat): 1613, 1320, 1249, 1162, 1103, 1076, 1064, 1016, 834 cm^{-1}. HRMS (ESI): *m*/*z* [M + H] calcd for $C_{33}H_{24}F_6N_3O$: 592.18181; found: 592.18163.