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Efficient and Practical Synthesis of 4(5)-Aryl-1*H*-imidazoles and 2,4(5)-Diaryl-1*H*-imidazoles via Highly Selective Palladium-Catalyzed Arylation Reactions

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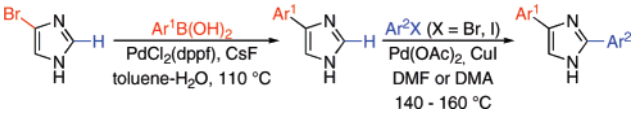
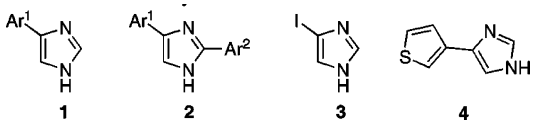


4(5)-Aryl-1*H*-imidazoles can be efficiently and selectively prepared by $PdCl_2$(dppf)-catalyzed Suzuki−Miyaura reaction of commercially available 4(5)-bromo-1*H*-imidazole with arylboronic acids under phase-transfer conditions. On the other hand, N-unprotected 4(5)-aryl-1*H*-imidazoles can undergo highly selective $Pd(OAc)_2$-catalyzed and CuI-mediated direct C-2-arylation with a variety of aryl bromides and iodides under base-free and ligandless conditions to produce 2,4(5)-diaryl-1*H*-imidazoles in modest to good yields. No N-arylation byproducts are observed under the experimental conditions used to prepare 2,4(5)-diaryl-1*H*-imidazoles.

Imidazoles aryl-substituted in the 4(5)-position are central structures of many compounds that elicit important biological and pharmacological responses. 4(5)-Aryl-1*H*-imidazoles **1**, for example, include compounds which display good in vitro antifungal activity,[1] are potent β-glucosidase inhibitors,[2] or exhibit activin receptor-like kinase 5 (ALK5) inhibitory activity,[3] and several 4(5)-aryl-2-heteroaryl-1*H*-imidazoles show NPY5 receptor antagonist activity.[4] On the other hand, 2-alkyl-4(5)-aryl-1*H*-imidazoles include potent Na^+ channel blockers,[5] and several 4(5)-aryl-5(4)-(4-fluorophenyl)-1*H*-imidazole derivatives are p38 MAP kinase inhibitors.[6] As a consequence, much attention has been paid to the development of efficient methods for preparation of 4(5)-aryl-substituted imidazole derivatives.[6d,7,8] Nevertheless, there are relatively few methods for the synthesis of imidazoles **1** and 2,4(5)-diaryl-1*H*-imidazoles **2**. Moreover, these synthetic protocols suffer from being multistep syntheses, providing modest yields and/or requiring commercially unavailable and/or expensive reagents. In particular, compounds **1** have been synthesized in modest yields via base-induced cycloaddition of tosylmethyl isocyanide to *N*-(dimethylsulfamoyl)-aldimines or *N*-tosylaldimines[9] or via Pd-catalyzed reaction of aryl halides or triflates with 1-tritylimidazol-4-yltin and -zinc reagents prepared from 1-trityl-4-iodoimidazole by Grignard formation followed by transmetalation.[10]



More recently, 4(5)-(3-thienyl)-1*H*-imidazole (**4**) has been prepared in 85% yield by Suzuki reaction of 3-thiopheneboronic acid with N-unprotected 4(5)-iodo-1*H*-imidazole (**3**).[11] However, **3** is commercially unavailable and can be prepared in 70% yield via polyiodination of imidazole followed by partial deiodination with $Na_2S_2O_3$.[12] On the other hand, imidazoles **2** have been often synthesized by condensating α-bromoketones with amidines[13] or formamide,[14] but these reactions were not always successful and sometimes gave low yield.[14] Compounds **2** have been also prepared in 13−42% overall yields via a three-step sequence involving the Suzuki reaction of 5-iodo-1-methoxymethyl-2-phenyl-1*H*-imidazole (**5**) or via a five-step process in which a key step is the Suzuki reaction of 2,4,5-tribromo-1-SEM-1*H*-imidazole (**6**).[15] Finally, 2,4(5)-diaryl-1*H*-imidazoles **2** have been very recently synthesized by treatment of arylglyoxals with arylaldehydes and ammonium acetate in methanol at room

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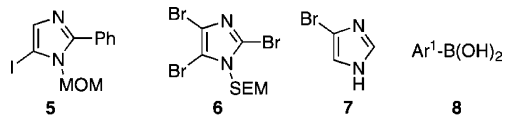
temperature.[16] However, the potential of this method is limited by the fact that arylglyoxals, save phenylglyoxal hydrate, are commercially unavailable; moreover, this approach involves the formation of significant amounts of byproducts consisting of 2-aroyl-4(5)-aryl-1*H*-imidazoles.[16]



5 **6** **7** **8**

In our continuing studies of the synthesis of arylazole derivatives,[17] we were interested in the development of concise and efficient novel approaches for preparation of monosubstituted 4(5)-aryl-1*H*-imidazoles **1** and disubstituted 2,4(5)-diaryl-1*H*-imidazoles **2** from cheap, commercially available starting materials. Herein, we report an efficient and general entry to imidazoles **1**, which utilizes a Pd-catalyzed Suzuki−Miyaura-type reaction between commercially available 4(5)-bromo-1*H*-imidazole (**7**) and arylboronic acids **8** under phase-transfer conditions.[18,19] Moreover, we describe the successful use of activated and unactivated aryl bromides and iodides in the synthesis of 2,4(5)-diaryl-1*H*-imidazoles **2** by Pd-catalyzed and Cu-mediated direct C-2-arylation of N-unprotected compounds **1** under base-free and ligandless conditions. It should be noted that we had previously employed similar reaction conditions for the efficient and highly regioselective direct C-2-arylation of a large variety of azoles, which included 1-aryl-1*H*-imidazoles, 1-methyl- and 1-benzyl-1*H*-imidazole, thiazole, oxazole, benzothiazole, and free (NH)-imidazole, -benzimidazole, and -indole.[17a,c,20]

Our initial investigations were focused to the preparation of imidazoles **1** by direct C-5-arylation of free (NH)-imidazole with aryl iodides in DMF at 140 °C in the presence of 2 equiv of a base such as Cs_2CO_3 or KOAc and a catalyst system consisting of 5 mol % of $Pd(OAc)_2$ and 10 mol % of tris(2-furyl)phosphine or 20 mol % of PPh_3, but, to our disappointment, no expected arylation product was obtained.

Searching for an alternative synthetic route, we speculated that imidazoles **1** might be conveniently prepared by a Suzuki−Miyaura reaction between N-unprotected bromoimidazole **7** and arylboronic acids **8**. However, a model reaction of **7** with phenylboronic acid (**8a**), which was performed according to a procedure previously employed to prepare **4** from iodide **3** and 3-thienylboronic acid, that is, in DMF at 80 °C for 24 h in the presence of 5 mol % of $Pd(PPh_3)_4$ and 2 equiv of aqueous Na_2CO_3,[11] afforded only traces of the required 4(5)-phenyl-1*H*-imidazole (**1a**). With this in mind, we thought it right to try a Suzuki-type coupling under phase-transfer conditions according to a procedure similar to that we previously employed for the selective C-4-arylation of 3,4-dichloro-2(5*H*)-furanone with arylboronic acids.[19a] We were then pleased to find that, when **7** was reacted with 2 equiv of phenylboronic acid (**8a**) in a 1:1 mixture of toluene and water for 91 h at 110 °C in the presence of 5 mol % of $PdCl_2(PPh_3)_2$, 5 mol % of benzyltriethylammonium chloride, and 3 equiv of CsF, the required 4(5)-phenyl-1*H*-imidazole **1a** was obtained in 66% yield (entry 1, Table 1). Moreover, a very similar reaction of **7** with 4-chlorophenylboronic acid (**8b**) for 139 h at 110 °C gave **1b** in 62% yield (entry 2, Table 1). Unfortunately, this protocol proved to be accompanied by an undesirable side reaction due to the aryl−aryl interchange between palladium- and phosphine-bound phenyl groups,[21] which, in the case of the synthesis of **1b**, led to small amounts of the phenyl coupling product **1a**. Nevertheless, this side reaction did not occur when $PdCl_2$(dppf) was used as the catalyst precursor in place of $PdCl_2(PPh_3)_2$. Furthermore, the use of $PdCl_2$(dppf) for the preparation of **1a** and **1b** caused higher yields and a significant reduction in the reaction time (compare entries 3 and 4 with entries 1 and 2, respectively, Table 1).

TABLE 1. Synthesis of 4(5)-Aryl-1*H*-imidazoles 1 via Pd-Catalyzed Reaction of 4(5)-Bromo-1*H*-imidazole (7) with Arylboronic Acids 8[a]

	Ar^1-B(OH)$_2$			Product	
entry	8	Ar^1	reaction time (h)	1	yield[b] (%)
1[c]	**8a**	C_6H_5	91	**1a**	66
2[c]	**8b**	4-ClC_6H_4	139	**1b**	62
3	**8a**	C_6H_5	65	**1a**	66
4	**8b**	4-ClC_6H_4	48	**1b**	82
5	**8c**	4-MeOC_6H_4	66	**1c**	91
6	**8d**	4-AcC_6H_4	72	**1d**	83
7	**8e**	2-naphthyl	72	**1e**	90
8	**8f**	2,5-$(MeO)_2C_6H_3$	72	**1f**	76
9	**8g**	benzo[*d*][1,3]-dioxol-5-yl	72	**1g**	86
10	**8h**	2-(CHO)C_6H_4	72	**1h**	0

[a] Unless otherwise noted, the reactions were run with 1 mmol of **7**, 2 mmol of **8**, 5 mol % of $PdCl_2$(dppf), 5 mol % of $BnEt_3NCl$, and 3 equiv of CsF in 14 mL of a 1:1 mixture of toluene and water at 110 °C (oil bath temperature). [b] Isolated yields. [c] This reaction was run with 5 mol % of $PdCl_2(PPh_3)_2$.

Having successfully demonstrated the viability of the $PdCl_2$(dppf)-catalyzed arylation of **7** with boronic acids **8a** and **8b**, we then tested the scope and limitation of this reaction by applying the reaction conditions of entries 3 and 4 of Table 1 to the synthesis of compounds **1** from **7** and commercially available boronic acids **8c**−**h**. The reactions involving **8c**−**g** proved to be clean and, as shown in Table 1, gave the required imidazole derivatives in high yields (entries 5−9). Nevertheless, the Pd-catalyzed reaction of **7** with 2-formylboronic acid (**8h**) did not produce the required imidazole **1h**. On the contrary, a

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TABLE 2. Pd-Catalyzed and Cu-Mediated C-2-Arylation of 4(5)-Aryl-1*H*-imidazoles 1 with Aryl Halides 9

	Reagents						Product	
entry[a]	**1**	Ar^1	**9**	Ar^2	X	reaction time (h)	**2**	yield[b] (%)
1	**1a**	C_6H_5	**9a**	4-$MeOC_6H_4$	I	72	**2a**	47
2	**1a**	C_6H_5	**9b**	4-$MeOC_6H_4$	Br	144	**2a**	30
3	**1a**	C_6H_5	**9c**	4-$CF_3C_6H_4$	I	68	**2b**	73
4	**1a**	C_6H_5	**9d**	4-$NO_2C_6H_4$	Br	48	**2c**	78
5	**1a**	C_6H_5	**9e**	3,4,5-$(MeO)_3C_6H_2$	I	72	**2d**	57
6	**1a**	C_6H_5	**9f**	2-naphthyl	Br	66	**2e**	62
7	**1e**	2-naphthyl	**9g**	4-$EtOOCC_6H_4$	Br	66	**2f**	40
8	**1c**	4-$MeOC_6H_4$	**9c**	4-$CF_3C_6H_4$	I	66	**2g**	42
9	**1b**	4-ClC_6H_4	**9c**	4-$CF_3C_6H_4$	I	88	**2h**	48

[a] The reactions were run with 1 mmol of **1**, 2 mmol of **9**, 5 mol % of $Pd(OAc)_2$, and 2 mmol of CuI in DMF at 140 °C (oil bath temperature) for X = I or in DMA at 160 °C (oil bath temperature) for X = Br. [b] Isolated yields.

large amount of benzaldehyde, derived from protodeboronation of **8h**, was present in the final reaction mixture. In our opinion, this result could be explained taking into account that (i) usually electron-deficient arylboronic acids such as **8h** tend to be difficult coupling partners as they are poorly nucleophilic and undergo transmetalation at a slower rate than electron-rich or -neutral arylboronic acids,[22] and (ii) transmetalation processes are very sensitive to steric factors.[22]

Having secured good access to compounds **1**, we then turned our attention to their conversion into 2,4(5)-diaryl-1*H*-imidazoles **2** by direct C-2-arylation.

In particular, we explored the synthesis of compounds **2** by $Pd(OAc)_2$-catalyzed and CuI-mediated direct arylation of imidazoles **1** with aryl bromides and iodides under base-free and ligandless conditions.[17a,c] In this context, it appeared particularly interesting to attempt the use of activated and unactivated aryl bromides as electrophiles since these compounds are cheaper than the corresponding iodides. Despite progress that has been made in Pd-catalyzed direct arylation of azoles with aryl bromides,[17a,e,f,23] evidence would suggest that these halides would work in Pd-catalyzed direct arylation of free (NH)-imidazole and -benzimidazole.[24] Table 2 summarizes representative results for the C-2-arylation of 4(5)-aryl-1*H*-imidazoles **1** with unactivated and activated aryl bromides and iodides **9**. It should be noted that the reactions involving aryl bromides (entries 2, 4, 6, and 7, Table 2) were performed in DMA at 160 °C, but those involving aryl iodides (entries 1, 3, 5, 8, and 9, Table 2) were run in DMF at 140 °C. In fact, it is well-precedented that oxidative addition into a C−X bond, which represents a key step of the mechanism of the Pd-catalyzed direct arylation reactions[25] and is commonly assumed as the turnover-limiting step,[26] is most facile for aryl iodides[27] and, thus, it requires milder experimental conditions. Remarkably, these arylation reactions proved to be clean and occurred with complete C-2 selectivity. In fact, no product of N-arylation or diarylation of 4(5)-aryl-1*H*-imidazoles **1** was observed under the experimental conditions used to prepare 2,4(5)-diaryl-1*H*-imidazoles **2**.

As shown in Table 2, aryl bromides with electron-withdrawing and electron-donating groups were compatible, and the C-2-arylation reactions furnished imidazoles **2** in modest to good yields. It should also be noted that the reaction between **1e** and activated aryl bromide **9g** (entry 7, Table 2) gave the required imidazole **2f** in a yield (40%) unexpectedly lower than that of the reaction of **1a** with unactivated aryl bromide **9f** in which imidazole **2e** was obtained in 62% yield (entry 6, Table 2).

In conclusion, we have established an efficient and selective protocol for the one-step synthesis of 4(5)-aryl-1*H*-imidazoles from commercially available 4(5)-bromo-1*H*-imidazole. We have also found that 4(5)-aryl-1*H*-imidazoles are able to undergo highly selective Pd-catalyzed and Cu-mediated direct C-2-arylation with unactivated and activated aryl iodides and bromides to give the required 2,4(5)-diaryl-1*H*-imidazoles in modest to good yields. In our opinion, these simple, convenient, and reliable procedures will enable efficient access to a variety of pharmacologically significant imidazole derivatives.

Investigations to elucidate the mechanism of the Pd-catalyzed and Cu-mediated direct C-2-arylation of azoles including imidazoles with aryl halides are in progress.

Experimental Section

General Procedure for the Synthesis of 4(5)-Aryl-1*H*-imidazoles 1a−g. A deaerated mixture of 4(5)-bromo-1*H*-imidazole (**7**) (0.147 g, 1.0 mmol), an arylboronic acid **8** (2.0 mmol), CsF (0.456 g, 3.0 mmol), $PdCl_2$(dppf) (0.041 g, 0.05 mmol), and $BnEt_3NCl$ (0.011 g, 0.05 mmol) in toluene (7 mL) and water (7 mL) was refluxed under argon for the period of time reported in Table 1. After completion of the reaction (48−72 h), the mixture was cooled to room temperature and partitioned between water and AcOEt, and the organic extract was dried and concentrated under reduced pressure. The residue was purified by MPLC on silica gel to provide the desired product. This procedure was used to prepare compounds **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, and **1g** in 66, 82, 91, 83, 90, 76, and 86%

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(27) For a discussion, see: (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047. (b) Grushin, V. V.; Alper, H. *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 193−226.

yield, respectively. Imidazole **1f** is representative of those prepared using this procedure.

4(5)-(2,5-Dimethoxyphenyl)-1*H*-imidazole (1f). The crude reaction product obtained in entry 8 of Table 1 by Pd-catalyzed Suzuki−Miyaura reaction of **7** and 2,5-dimethoxyphenylboronic acid (**8f**) was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (93:7) as eluent to give **1f** (0.155 g, 76%) as a red solid: mp 97−100 °C; ^{1}H NMR (200 MHz, CD_3OD) δ 7.71 (s, 1H), 7.55 (s, 1H), 7.45 (d, J = 3.0 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 6.77 (dd, J = 9.0 and 3.0 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (50.3 MHz, CD_3OD) δ 155.3, 151.6, 136.9, 136.1, 123.1, 121.3, 113.8, 113.6, 113.3, 56.4, 56.1; EI-MS *m*/*z* 205 (13), 204 (100), 203 (17), 189 (34), 169 (97). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.61; H, 5.84; N, 13.58. GLC analysis showed that **1f** had chemical purity higher than 98%.

General Procedure for the Palladium-Catalyzed and Copper-Mediated Synthesis of 2,4(5)-Diaryl-1*H*-imidazoles 2a−h. A compound **1** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), CuI (0.38 g, 2.0 mmol), and an aryl halide **9** (2.0 mmol) were placed in the reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated twice. When the reaction involved an aryl iodide, deaerated DMF (5 mL) was then added by syringe under a stream of argon at room temperature, and the resulting mixture was stirred at 140 °C under argon for the period of time reported in entries 1, 3, 5, 8, and 9 of Table 2. However, when the reaction involved an aryl bromide, DMA (5 mL) was added by syringe in place of DMF, and the resulting mixture was stirred under argon at 160 °C for the period of time reported in entries 2, 4, 6, and 7 of Table 2. The degree of completion of the reaction was established by GLC and GLC−MS analysis of a sample of the crude reaction mixture after treatment with a saturated aqueous NH_4Cl solution and extraction with AcOEt. After being cooled to 20 °C, the reaction mixture was diluted with AcOEt and poured into a saturated aqueous NH_4Cl solution. The resulting mixture was basified with a few drops of aqueous NH_4OH, stirred in the open air for 0.5 h, and then extracted with AcOEt. The organic extract was washed with water, dried, and concentrated under reduced pressure, and the residue was purified by MPLC on silica gel. The chromatographic fractions containing the required compound were collected and concentrated. This procedure was employed to prepare 2,4(5)-diaryl-1*H*-imidazoles **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, and **2h** in 47, 73, 78, 57, 62, 40, 42, and 48% yield, respectively. 4(5)-Phenyl-2-[(4-trifluoromethyl)phenyl]-1*H*-imidazole (**2b**) is representative of those prepared using this procedure.

4(5)-Phenyl-2-[(4-trifluoromethyl)phenyl]-1*H*-imidazole (2b). The crude product obtained in entry 3 of Table 2 from the Pd-catalyzed and Cu-mediated reaction between **1a** and 4-iodobenzotrifluoride (**9c**) was purified by MPLC on silica gel with a mixture of toluene and AcOEt (80:20 + 0.1% Et_3N) as eluent to give **2b** (0.210 g, 73%) as colorless solid: mp 174−176 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.22 (br s, 1H), 7.85 (m, 2H), 7.70 (m, 2H), 7.46 (m, 2H), 7.32 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 145.8, 139.7, 132.8, 131.8, 130.8, 130.1, 128.9 (2C), 127.6, 125.8 (2C), 125.7 (2C), 125.2 (2C), 118.3; EI-MS *m*/*z* 289 (18), 288 (100), 287 (7), 90 (10), 89 (10). Anal. Calcd for $C_{16}H_{11}F_3N_2$: C, 66.66; H, 3.85; N, 9.72. Found: C, 66.57; H, 3.79; N, 9.64. GLC analysis showed that **2b** had chemical purity higher than 98%.

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Supporting Information Available: Experimental procedures and characterization for compounds **1a−e**, **1g**, **2a**, and **2c−h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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