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Completely N^1-Selective Palladium-Catalyzed Arylation of Unsymmetric Imidazoles: Application to the Synthesis of Nilotinib

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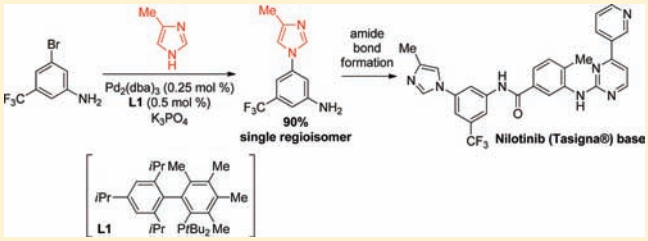
Supporting Information

ABSTRACT: The completely N^1-selective Pd-catalyzed arylation of unsymmetric imidazoles with aryl halides and triflates is described. This study showed that imidazoles have a strong inhibitory effect on the in situ formation of the catalytically active Pd(0)−ligand complex. The efficacy of the N-arylation reaction was improved drastically by the use of a preactivated solution of $Pd_2(dba)_3$ and **L1**. From these findings, it is clear that while imidazoles can prevent binding of **L1** to Pd, once the ligand is bound to the metal, these heterocycles do not displace it. The utility of the present catalytic system was demonstrated by the regioselective synthesis of the clinically important tyrosine kinase inhibitor nilotinib.



INTRODUCTION

4-Substituted N^1-arylimidazoles represent key structural motifs in medicinally important compounds, including tyrosine kinase inhibitors,[1] γ-secretase modulators,[2] serotonin receptor antagonists,[3] and glycine transporter type-1 inhibitors (Figure 1).[4]

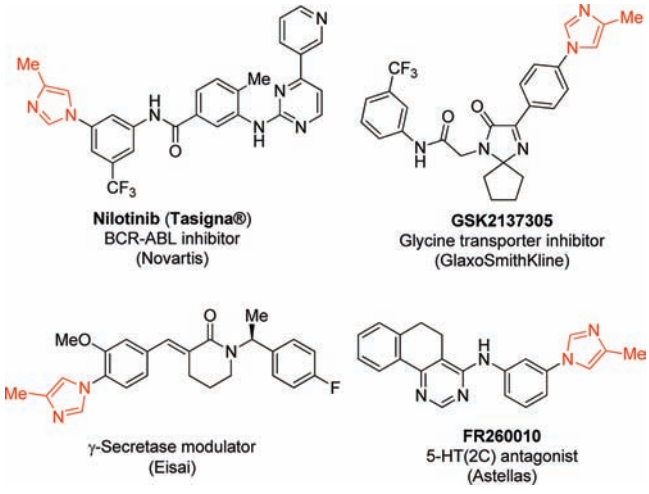


Figure 1. Biologically active compounds containing the *N*-arylimidazole motif.

Traditionally, *N*-arylimidazoles have been prepared via an S_NAr process or classical Ullmann-type coupling with stoichiometric copper. In the former case, aryl donors are limited to aryl halides with strongly electron-withdrawing groups or activated heteroaryl halides.[5] The classical Ullmann coupling has a broader substrate scope; however, the reaction requires a long reaction time at high temperature (150−200 °C), which limits its functional group tolerance. Over the past decade, there has been remarkable progress in the development of Cu-catalyzed methods for N-arylation of imidazoles with aryl halides[6] or arylboronic acids.[7] Because of its broad scope under mild conditions along with the low cost and low toxicity of copper salts, the Cu-catalyzed N-arylation method quickly found many applications in medicinal chemistry and material science fields.[8] However, because of the tautomeric nature of unsymmetric 1*H*-imidazoles, the Cu-catalyzed arylation and S_NAr reactions of 4-substituted imidazoles oftentimes give poor to moderate regioselectivities.[9] In addition, the similar physical properties of the N^1-aryl and N^3-aryl regioisomers oftentimes make separation of the products difficult. Therefore, the development of general catalytic methods that selectively produce the N^1-arylated product from tautomeric 4-substituted imidazoles, while challenging, would be particularly valuable.[10]

During the past few decades, extensive effort from different groups has led to the discovery of a wide variety of Pd-catalyzed methods for the formation of C−N bonds in aromatic systems.[11] Although the Pd-catalyzed N-arylation of a variety of nitrogen nucleophiles including amines/anilines,[12] imines,[13] amides,[14] indoles,[15] hydrazine,[16] hydrazones,[17] ammonia,[18] and nitrite[19] has been well-documented, the corresponding N-arylation of imidazoles is still not satisfactory; only a few reports of Pd-catalyzed N-arylation of imidazoles have appeared, and these have mostly been applied to a small number of activated aryl bromides and chlorides.[20] In 2006, our group reported the Pd-catalyzed N-arylation of imidazole with unactivated aryl bromide (4-bromotoluene) using biaryl phosphine **L1**.[21] However, the reaction requires relatively high catalyst loadings (5 mol % Pd and 10 mol % **L1**) and gives the N-arylated product in only a moderate yield even after 24 h. In addition,

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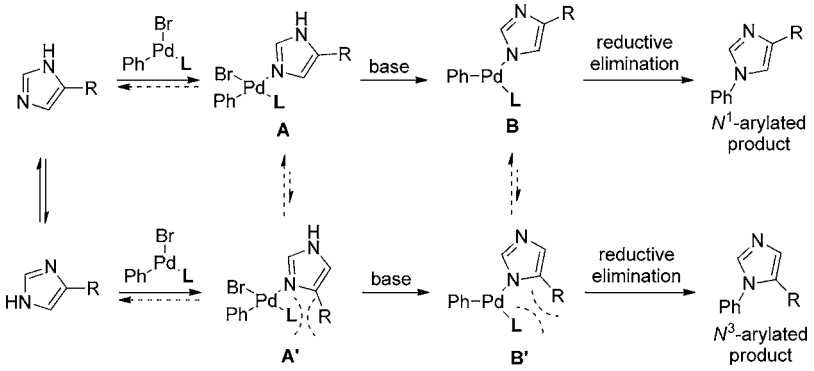
Scheme 1. Presumed Intermediates in the Pd-Catalyzed N-Arylation of 4-Substituted Imidazoles



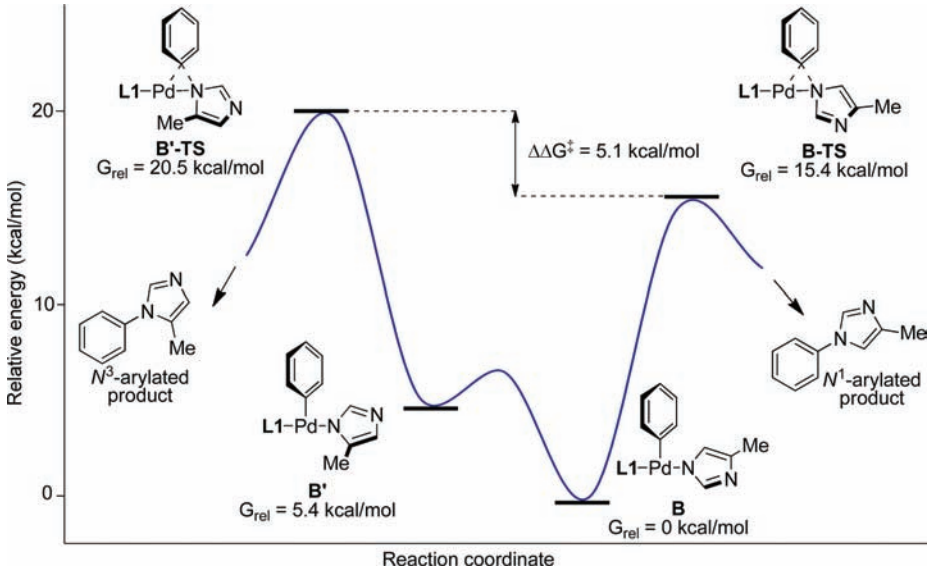


Figure 2. Energy diagram for reductive elimination with **L1**.

reactions of 4-substituted imidazoles, functionalized aryl halides, and heteroaryl halides were not disclosed. Herein we report a full account of our investigations of completely N^1-selective arylation of imidazoles and disclose a significantly improved Pd-catalyzed protocol. The usefulness of the completely N^1-selective arylation of unsymmetric 4-substituted imidazoles was demonstrated by the regioselective syntheses of the medicinally important compounds GSK2137305 and nilotinib.

RESULTS AND DISCUSSION

Design and Development of the Completely N^1-Selective Arylation of 4-Methylimidazole. Scheme 1 shows some of the presumed intermediates in the Pd-catalyzed N-arylation of 4-substituted imidazoles.

We reasoned that selective formation of the N^1-arylated product might be achievable as a result of unfavorable steric interactions in **B′** relative to **B**. The idea was supported by density functional theory (DFT) calculations with **L1**; complex **B** was favored over complex **B′**, and the corresponding transition states for the reductive elimination (**B-TS** and **B′-TS**) were also significantly different in energy ($\Delta\Delta G^{\ddagger}$ = 5.1 kcal/mol) in favor of the transition state for the N^1-arylated product (Figure 2).

To test the above hypothesis, we investigated the N-arylation of 4-methylimidazole with bromobenzene using a variety of phosphine ligands (Table 1). An examination of reaction conditions revealed that the use of $Pd_2(dba)_3$ (0.75 mol %), **L1** (1.8 mol %), and K_3PO_4 selectively produced the N^1-arylated product, albeit in only 6% yield (entry 1). The examination of other structurally related biaryl phosphine ligands (**L2**−**L5**) and bases (Cs_2CO_3, K_2CO_3, NaO*t*Bu) provided no improvement in the reaction efficacy (entries 2−8). Similarly, we obtained no N-arylation product with **L6**, **L7**, or **L8** (entries 9−11), which were previously employed for the N-arylation of unsubstituted imidazole with activated aryl bromides[20a] and chlorides,[20b] in the presence of $Pd(OAc)_2$ using the reported protocol published for each of these ligands. Further experimentation using **L1** revealed that an improved yield (66%) could be obtained by employing a higher catalyst loading (5 mol % Pd and 10 mol % **L1**); however, the reaction was sluggish, and full conversion of bromobenzene was not achieved even after 20 h (entry 12). Since imidazoles are known to be ligands in Pd(0)-catalyzed reactions,[22] we suspected that the ineffectiveness of the reaction might arise from prevention of the in situ formation of the catalytically active phosphine-ligated Pd(0) complex by excess 4-methylimidazole. Thus, we heated a premixed solution of $Pd_2(dba)_3$ and **L1** in the solvent for 3 min at 120 °C prior to the injection to other reagents. With this protocol, the preactivated catalyst solution [$Pd_2(dba)_3$/**L1**] showed high activity, affording the N^1-arylated product in 97% GC yield (95% isolated yield) in 5 h with 1.5 mol % Pd and 1.8

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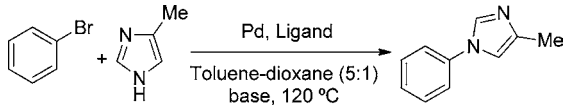
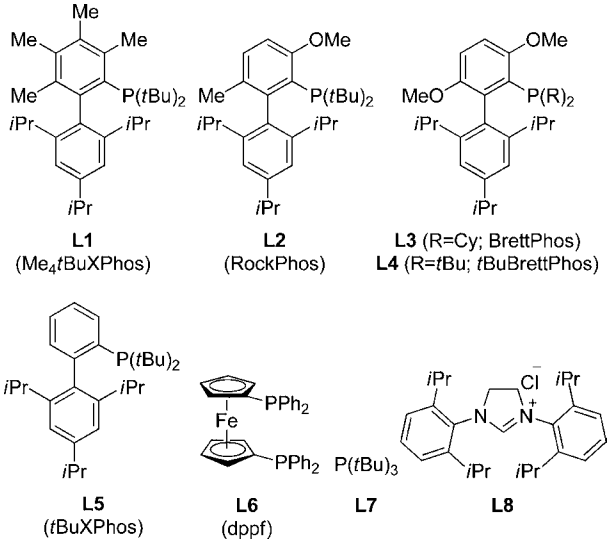
Table 1. Ligand Effects on Pd-Catalyzed N-Arylation of 4-Methylimidazole[a]

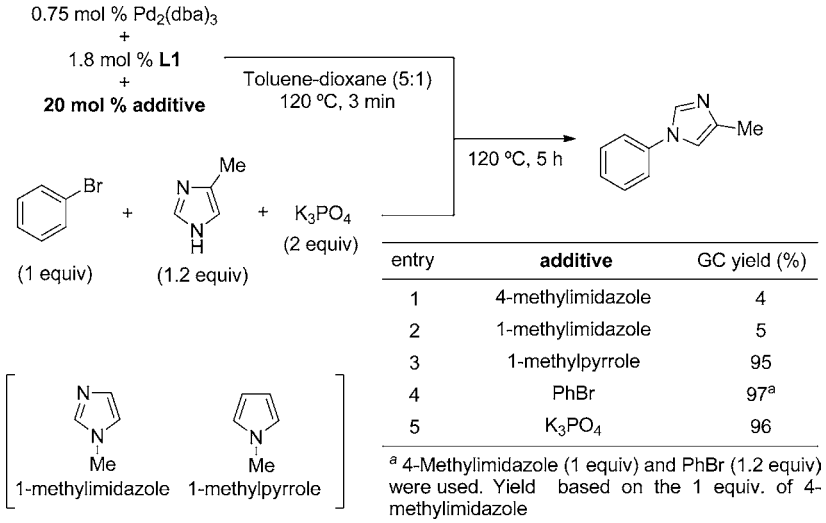


entry	Pd source (mol %)	ligand (mol %)	base	time (h)	GC conv. (%)	GC yield (%)
1	$Pd_2(dba)_3$ (0.75)	**L1** (1.8)	K_3PO_4	20	8	6
2	$Pd_2(dba)_3$ (0.75)	**L2** (1.8)	K_3PO_4	20	6	3
3	$Pd_2(dba)_3$ (0.75)	**L3** (1.8)	K_3PO_4	20	5	0
4	$Pd_2(dba)_3$ (0.75)	**L4** (1.8)	K_3PO_4	20	5	0
5	$Pd_2(dba)_3$ (0.75)	**L5** (1.8)	K_3PO_4	20	3	0
6	$Pd_2(dba)_3$ (0.75)	**L1** (1.8)	Cs_2CO_3	20	3	0
7	$Pd_2(dba)_3$ (0.75)	**L1** (1.8)	K_2CO_3	20	3	0
8	$Pd_2(dba)_3$ (0.75)	**L1** (1.8)	NaO*t*Bu	20	9	0
9[b]	$Pd(OAc)_2$ (5)	**L6** (10)	KO*t*Bu	0.25	8	0
10[c]	$Pd(OAc)_2$ (2)	**L7**(2)	NaO*t*Bu	24	6	0
11[d]	$Pd(OAc)_2$ (2)	**L8** (2)	NaO*t*Bu	12	9	0
12	$Pd_2(dba)_3$ (2.5)	**L1** (10)	K_3PO_4	20	69	66
13[e]	$Pd_2(dba)_3$ (0.75)	**L1** (1.8)	K_3PO_4	5	100	97 (95[f])

[a]Conditions for entries 1−8, 12, and 13: bromobenzene (1 mmol), 4-methylimidazole (1.2 mmol), base (2 mmol), $Pd_2(dba)_3$ (0.75 or 2.5 mol %), ligand (1.8 or 10 mol %), toluene−dioxane (5:1, 1.0 mL), 120 °C, 5 or 20 h. [b]Reaction was performed in DMF (2 mL) under microwave heating (180 °C for 15 min). [c]Reaction was performed in *o*-xylene (20 mL) at 120 °C for 24 h. [d]Reaction was performed in THF (20 mL) at room temperature for 12 h. [e]$Pd_2(dba)_3$ and **L1** were premixed in the solvent at 120 °C for 3 min. [f]Isolated yield.



Scheme 2. Inhibitory Effect of Imidazoles on the Pd-Catalyzed N-Arylation of 4-Methylimidazole



entry	**additive**	GC yield (%)
1	4-methylimidazole	4
2	1-methylimidazole	5
3	1-methylpyrrole	95
4	PhBr	97[a]
5	K_3PO_4	96

[a] 4-Methylimidazole (1 equiv) and PhBr (1.2 equiv) were used. Yield based on the 1 equiv. of 4-methylimidazole

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mol % **L1** (entry 13).[23,24] To understand further the source of inhibition of the reaction (entry 1 vs 13), imidazoles and each of the reaction components (K_3PO_4 and PhBr) were, in separate experiments, added to the premixed solution of $Pd_2(dba)_3$ and **L1** (Scheme 2). When the catalyst premixing was peformed in the presence of 4-methylimidazole, the reaction was significantly less efficient, and the product was obtained in only 4% yield (Scheme 2, entry 1). Similarly, 1-methylimidazole showed an inhibitory effect on the reaction (entry 2). On the other hand, addition of 1-methylpyrrole, bromobenzene, or K_3PO_4 to the premixing solution did not significantly affect the reaction outcome, and the product was obtained in high yields (entries 3–5). To observe the effect of 4-methylimidazole on the in situ formation of the active catalyst, the ^{31}P NMR signal of **L1** was monitored during the catalyst premixing step (Figure 3). New phosphorus signals at

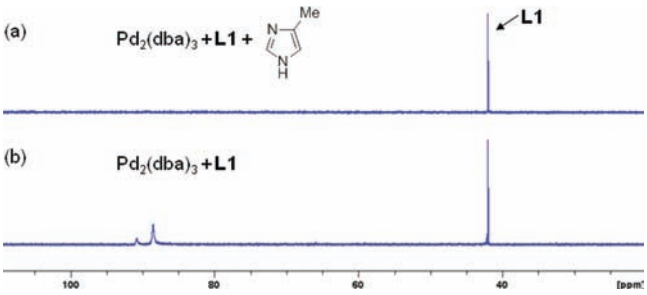

Figure 3. ^{31}P NMR spectra of the solution of **L1** and $Pd_2(dba)_3$ in the presence (a) or absence (b) of 4-methylimidazole (16 equiv relative to Pd).

88 and 91 ppm appeared after heating of **L1** and $Pd_2(dba)_3$ in toluene at 120 °C, for 3 min,[25] while only free **L1** was observed when **L1** and $Pd_2(dba)_3$ were heated in the presence of excess 4-methylimidazole, suggesting that 4-methylimidazole prevents in situ ligand binding to Pd(0). Overall, our investigation led to the following conclusions: (1) **L1** is a highly effective ligand for the Pd-catalyzed N-arylation of 4-methylimidazole; (2) imidazoles have an inhibitory effect on the in situ formation of the catalytically active Pd(0)–ligand complex, and therefore, **L1** and $Pd_2(dba)_3$ should be preheated together in the solvent before they are exposed to the imidazole. Of great significance is the fact that while 4-methylimidazole prevents the binding of **L1** to the Pd center, once the ligand is bound it is not displaced by the imidazole.

Substrate Scope of N-Arylation of 4-Substituted Imidazoles. With an optimized protocol in hand, we next investigated the scope of the N-arylation of unsymmetric imidazoles and benzimidazoles (Table 2). The Pd-catalyzed N^1-selective arylation was highly general, and a variety of functionalized aryl bromides and chlorides could be employed for the arylation of 4-methylimidazole (entries 1–9), 4-phenylimidazole (entries 12 and 13), *N*-acetylhistamine (entry 14), and 4-cyanomethylimidazole (entries 15 and 16) using 0.5–2.5 mol % Pd. In addition, aryl triflates were suitable substrates (entries 10 and 11). To the best of our knowledge, this is the first example of N-arylation of imidazole derivatives with aryl triflates. No N^3-arylated regioisomers were detected in any of the cases examined. The N-arylations of 4-substituted imidazoles with 3-halopyridines (entries 4 and 12), 2-bromopyridines (entries 8 and 15), and chloropyrazine (entry 16) demonstrate the utility of the method with heteroaryl substrates. Lastly, the N-arylation of 4-substituted benzimidazoles exclusively occurred at the less sterically hindered N^1 position to give N^1-arylated benzimidazoles in good yields (entries 17–18).

Synthesis of GSK2137305. GSK2137305 is a potent glycine transporter inhibitor developed by GlaxoSmithKline for the treatment of neurological disorders. Previously, N^1-aryl-4-methylimidazole **2** was synthesized by Cu-catalyzed N-arylation of 4-methylimidazole with aryl bromide **1a**. Although the Cu-catalyzed N-arylation proceeded under ligand-free conditions, an approximately 4:1 mixture of N^1- and N^3-arylated products was formed, and a yield of only 54% was obtained.[4] With 0.1 mol % $Pd_2(dba)_3$ and 0.2 mol % **L1**, N-arylation of 4-methylimidazole with aryl bromide **1a** gave **2** in 93% yield as a single regioisomer (Scheme 3). Alternatively, aryl chloride substrate **1b**, which was prepared from less expensive 4-chlorobenzaldehyde,[26] could be employed in the N-arylation reaction with 0.15 mol % $Pd_2(dba)_3$ and 0.3 mol % **L1**. Subsequent N-alkylation of **2** afforded GSK2137305 (**3**) in 82% yield.

Synthesis of Nilotinib (Tasigna). The usefulness of the Pd-catalyzed N^1-selective arylation of 4-substituted imidazoles was further demonstrated by the synthesis of the clinically important anticancer drug nilotinib (Scheme 4). Nilotinib (Tasigna) is a second-generation BCR-ABL tyrosine kinase inhibitor that shows greater efficacy than imatinib (Gleevec) in the treatment of chronic myelogenous leukemia (CML), including Gleevec-resistant patients.[1] In the previous syntheses of nilotinib, 4-methylimidazole was introduced by moderately regioselective reactions such as the S_NAr reaction with an aryl fluoride[27] or Cu-catalyzed N-arylation with an aryl bromide.[28,29] With 0.25 mol % $Pd_2(dba)_3$ and 0.5 mol % **L1**, key intermediate **5** was prepared from aryl bromide **4** in 90% yield as a single regioisomer. Use of excess 4-methylimidazole (2.4 equiv), a toluene–*t*BuOH mixed solvent, and lower concentration (0.5 M ArBr) were found to be important to suppress undesirable N-arylation of the aniline nitrogens of **4** and **5**. Ester **8** was prepared from aminopyrimidine **6** and aryl bromide **7** using 0.3 mol % BrettPhos (**L3**) precatalyst.[12b] Combining **5** and **8** gave nilotinib base **9** in 90% yield. Alternatively, 4-methylimidazole could be introduced in the last step of the synthesis using aryl bromide **10**, 1 mol % $Pd_2(dba)_3$ and 2.2 mol % **L1**. Again, the N-arylated product **9** was obtained as single regioisomer. This late-stage N-arylation route could potentially provide facile access to a large variety of nilotinib analogues.

■ CONCLUSION

On the basis of mechanistic considerations, we have established a catalytic method for the completely N^1-selective arylation of unsymmetric imidazoles with aryl bromides, chlorides, and triflates. This study has shown that imidazoles have a strong inhibitory effect on the in situ formation of the catalytically active Pd(0)–ligand complex. Heating $Pd_2(dba)_3$ and **L1** in the absence of imidazoles before the reaction prevented the inhibitory effect, and the efficacy of the N-arylation of imidazoles was improved drastically. From these findings, it is clear that while imidazoles can prevent binding of **L1** to the Pd, once the ligand is bound to the metal, these heterocycles do not displace it. These results also point to the importance, in general, of allowing the preparation of a catalyst (or, more accurately, the ligand–metal complex) to take place prior to exposure to substrates that otherwise would tightly bind the

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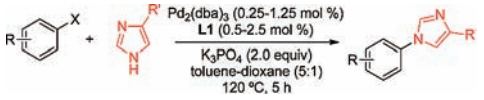
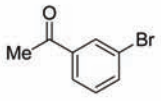
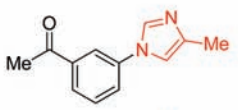
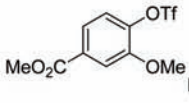
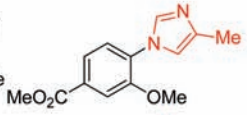
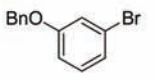
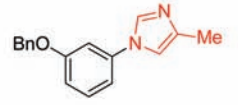
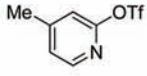
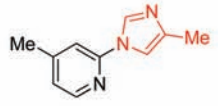
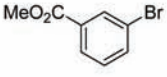
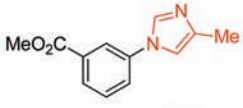
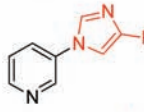
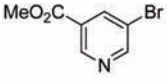
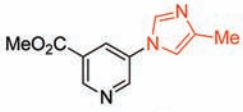
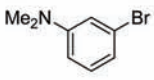
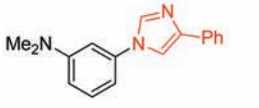
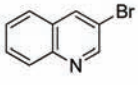
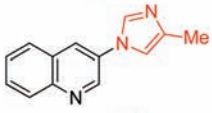
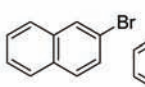
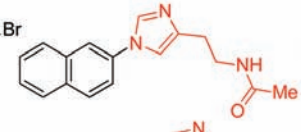
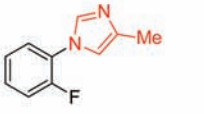
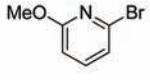
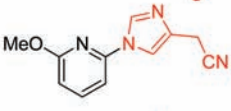
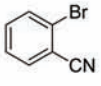
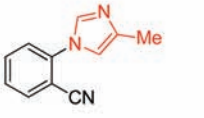
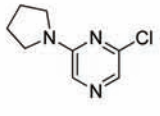
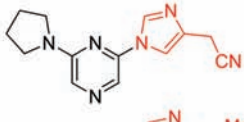
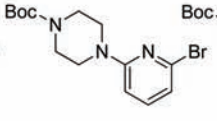
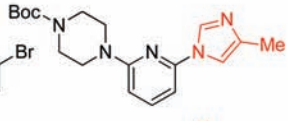
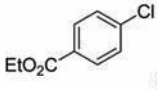
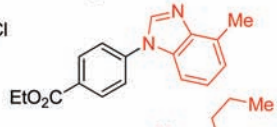
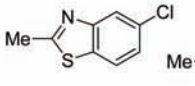
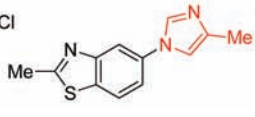
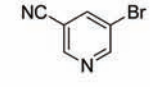
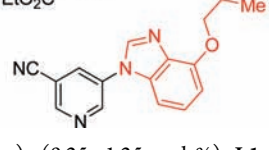
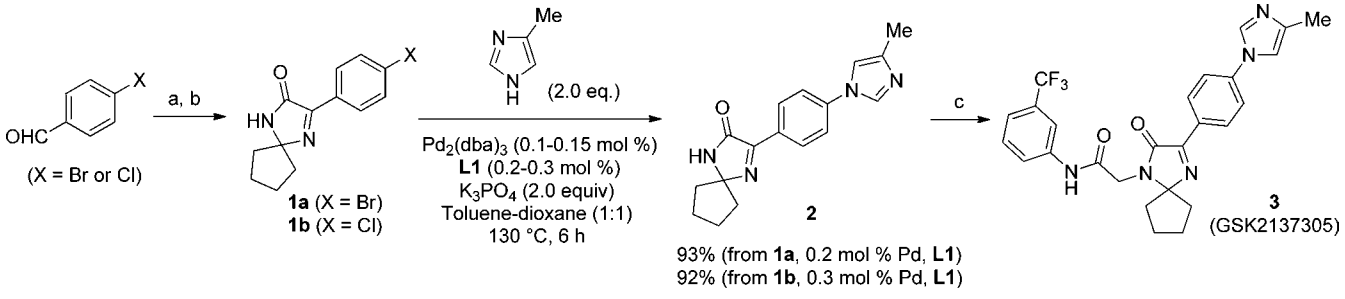
Table 2. Substrate Scope of the N^1-Selective Arylation of Unsymmetric Imidazoles[a]



entry	Ar-X	product	Pd (mol%)	yield (%)	entry	Ar-X	product	Pd (mol%)	yield (%)
1			1.5	84	10			1.5	77
2			0.5	93	11			1.5	80
3			0.5	91	12			1.5	89
4			1.5	85	13			1.5	96
5			0.5	94	14			1.5	95
6			1.5	94	15			1.5	90
7			2	88	16			2.5	92
8			2	80	17			1	90
9			1.5	79	18			1.5	86

[a]Conditions: Ar–X (1 mmol), 4-substituted imidazole (1.1–1.2 mmol), K_3PO_4 (2 mmol), $Pd_2(dba)_3$ (0.25–1.25 mol %), **L1** (0.5–2.5 mol %), toluene–dioxane (5:1, 1.0 mL), 120 °C, 5 h. $Pd_2(dba)_3$ and **L1** were premixed in the solvent at 120 °C for 3 min. Isolated yields representing averages of two runs are shown.

Scheme 3. Synthesis of GSK2137305[a]

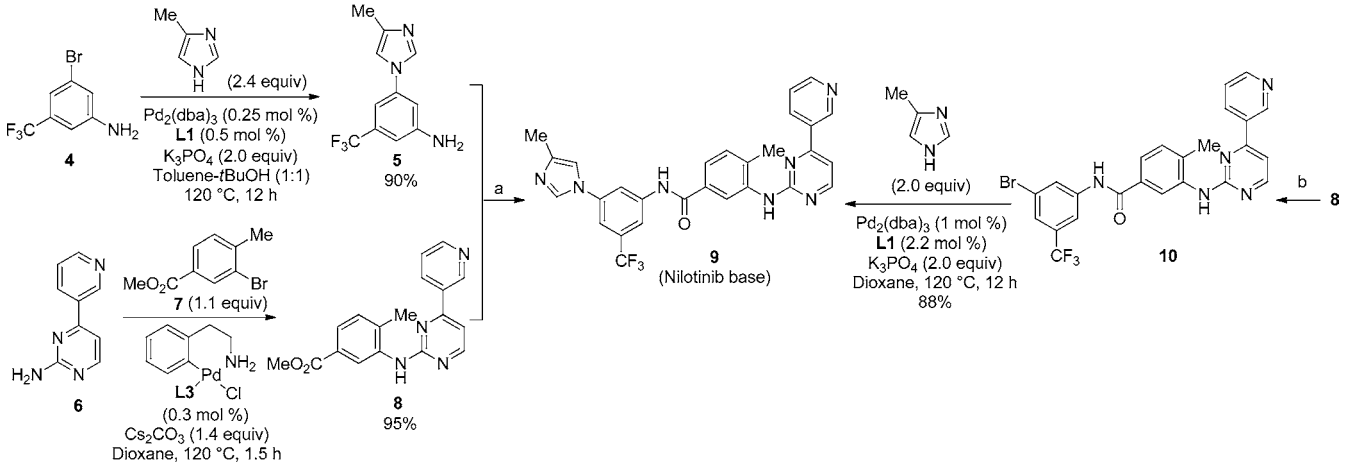


[a]Reagents and conditions: (a) NaCN (1.1 equiv), NH_4OAc (3.0 equiv), aq. NH_4OH, EtOH, rt, 4 h, then cyclopentanone (2.5 equiv), NaOEt (0.1 equiv), *n*-BuOH, 80 °C, 12 h; 38% (X = Br), 32% (X = Cl). (b) DDQ (1.1 equiv), EtOAc, 60 °C, 1 h; 89% (X = Br), 90% (X = Cl). (c) Chloroacetyl chloride (1.1 equiv), 3-aminobenzotrifluoride (1.15 equiv), KOH (2.5 equiv), NMP; 82%.

metal in question. The utility of this method has been demonstrated by the regiocontrolled syntheses of GSK2137305 and nilotinib. Highly N^1-selective couplings of 4-substituted imidazoles with aryl bromides, chlorides, and triflates using

dx.doi.org/10.1021/ja2102373 | J. Am. Chem.Soc. 2012, 134, 700–706

Scheme 4. Synthesis of Nilotinib Base[a]



[a]Reagents and conditions: (a) KO*t*Bu (5.5 equiv), THF, rt, 12 h; 90%. (b) **4** (1.05 equiv), KO*t*Bu (5.5 equiv), THF, rt, 12 h; 85%.

S_NAr or Cu-based systems have not been reported to date. Thus, the present Pd catalyst system complements existing S_NAr-based and Cu-catalyzed N-arylation methods. Studies of the Pd-catalyzed arylation of other five-membered nitrogen heterocycles are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Complete refs 1a and 20d, experimental procedures, product characterization, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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