Drug Discovery: Recent Progress and the Future

Communication to the Editor

Palladium-Catalyzed C–H Heteroarylation of 2,5-Disubstituted Imidazoles

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We developed a palladium-catalyzed C–H *N*-heteroarylation of *N*-protected-2,5-disubstituted imidazoles at the C4-position using *N*-heteroaryl halides as a coupling partner. Intensive reaction condition screening led us to identify fluorinated bathophenanthroline **7** as the optimum ligand for the palladium catalyst. This reaction will enhance lead optimization of drug candidates by facilitating the synthesis of heterobiaryl compounds containing an imidazole ring.

Key words palladium; C–H activation; imidazole; bathophen; drug lead optimization

Introduction

Traditional cross-coupling reactions using preactivated aryl substrates such as aryl boronates and arylzinc reagents are a reliable synthetic method for biaryl compounds. These methods, however, require the preparation of preactivated substrates, which increases the total number of synthetic steps, thereby hampering the streamlined synthesis of target molecules. Direct functionalization of unactivated C–H bonds of organic molecules requires no preactivation steps, and can thus facilitate the synthesis and structural optimization of functional organic compounds, including drugs, starting from readily available starting materials.^{1–10)}

In our studies toward the development of small-molecule aggregation inhibitors of amyloid β peptides (A β) as potential drugs to treat Alzheimer's disease,¹¹⁾ we became interested in the synthesis of biaryl compounds comprising a six-membered *N*-heterocycle and an imidazole ring. More generally, arylated imidazoles are a fundamental scaffold of various drug-lead molecules.^{12–20)} The synthesis of *N*-heteroarylated imidazoles via C–H activation, however, has not been systematically studied.

For previously reported C–H arylation catalysis of imidazoles, Fagnou developed C4–H arylation of 2,5-disubstituted imidazole *N*-oxides with aryl bromides using a Pd(OAc)₂/phosphine complex²¹⁾ (Chart 1a). Sames developed a formal C4-arylation through Pd(OAc)₂/phosphine-catalyzed C5–H arylation

of *N*-trimethylsilylethoxymethyl (SEM)-protected imidazoles, followed by migration of the SEM group to the sterically less-hindered nitrogen atom of the imidazole ring²²⁾ (Chart 1b). Because the C4-position is the least reactive carbon center on an imidazole ring, for both stereoelectronic and electrostatic reasons,²²⁾ the method is a unique entry to formal C4-selective functionalization of imidazoles. Shibahara and Murai reported a sequential C–H arylation of imidazoles catalyzed by a cationic palladium/phenanthroline complex.²³⁾ Their method can be used to introduce three distinct aryl groups to the three C–H bonds of *N*-protected imidazoles step-by-step in one pot^{24,25)} (Chart 1c). Here we report that a palladium pivalate (Pd(OPiv)₂)/4,7-*p*-fluorophenylphenanthroline (F-bathophen: **7**) complex is a good catalyst for C4–H activation of 2,5-disubstituted imidazoles, allowing for coupling with *N*-heteroaryl halides to produce C4 *N*-heteroarylated imidazoles (Chart 1d).

We initially applied the reaction conditions developed by Shibahara *et al.*²³⁾ using a 5 mol% cationic palladium/phenanthroline (phen) complex, [Pd(phen)₂](PF₆)₂, to the reaction between imidazole **1a** and 2-bromopyridine (**2a**) in dimethylacetamide (DMA) solvent. Despite the analogy in the reaction pattern to Shibahara and Murai's precedent, the desired heterobiaryl compound **3a** was not obtained at all (Table 1, entry 1).

a) Fagnou and coworkers²¹⁾ b) Sames and coworkers²²⁾ c) Shibahara, Murai, and coworkers²³⁾

d) This work

Chart 1. C–H Arylation of Imidazoles with Aryl Halides

(Color figure can be accessed in the online version.)

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Table 1. Reaction Condition Optimization^[a]

	1a : P = SEM 1b : P = MOM	2a (2 equiv)		3a : P = SEM 3b : P = MOM	
Entry	1a/1b	[Pd]	Ligand	Base	Yield [%]
1 ^[b]	1a	[Pd(phen) ₂](PF ₆) ₂		Cs ₂ CO ₃	0
2 ^[c,d]	1a	Pd(OAc) ₂	none	K ₂ CO ₃	0
3 ^[c,d]	1a	Pd(OAc) ₂	(p-F-C ₆ H ₄) ₃ P	K ₂ CO ₃	0
4 ^[c,d]	1a	Pd(OAc) ₂	BINAP	K ₂ CO ₃	10
5 ^[c]	1a	Pd(OAc) ₂	<i>t</i> BuBrettPhos	K ₂ CO ₃	13
6 ^[c]	1a	Pd(OAc) ₂	4	K ₂ CO ₃	11
7 ^[c]	1b	Pd(OAc) ₂	4	K ₂ CO ₃	11
8	1b	Pd(OAc) ₂	4	K ₂ CO ₃	33
9	1b	Pd(OAc) ₂	4	Cs ₂ CO ₃	34
10	1b	Pd(OAc) ₂	4	CsOAc	11
11	1b	Pd(OAc) ₂	4	CsOPiv	24
12	1b	Pd(OPiv) ₂	4	Cs ₂ CO ₃	33
13	1b	Pd(OAc) ₂	5	Cs ₂ CO ₃	12
14	1b	Pd(OPiv) ₂	6	Cs ₂ CO ₃	38
15	1b	Pd(OPiv) ₂	7	Cs ₂ CO ₃	50
16	1b	Pd(OPiv) ₂	8	Cs ₂ CO ₃	12
17 ^[e]	1b	Pd(OPiv) ₂	7	Cs ₂ CO ₃	50
18 ^[f]	1b	Pd(OPiv) ₂	7	Cs ₂ CO ₃	74

- 4**: R = Ph
5: R = H
6: R = p-CF₃C₆H₄
7: R = p-Fc₆H₄
8: R = p-OMeC₆H₄

[a] General conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), palladium complex (0.020 mmol), ligand (0.020 mmol), and base (0.20 mmol) were stirred in toluene (0.5 mL) at 120 °C for 7–24 h under argon. [b] The reaction was conducted in DMA solvent at 150 °C for 24 h using 5 mol% catalyst. [c] The reaction was conducted using 5 mol% Pd(OAc)₂ and 7.5 mol% ligand for 15 h. [d] The reaction was conducted in DMA solvent. [e] 2-Chloropyridine was used instead of **2a**. [f] 2-Iodopyridine was used instead of **2a**. (Color figure can be accessed in the online version.)

Next, we examined various conditions using Pd(OAc)₂/phosphine complexes (entries 2–5) by referring to the reports by Fagnou and colleagues,²¹⁾ and Sames and colleagues.²²⁾ Product **3a** was obtained in a maximum yield of 13% using *t*BrettPhos as the ligand and toluene as the solvent (entry 5). The yield of **3a** was comparable in either DMA or toluene, but formation of the byproduct bipyridine through reductive homo-coupling of **2a** was significantly suppressed in toluene. Thus, we selected toluene as the best solvent after entry 5. The use of bathophenanthroline **4** as the ligand slightly decreased the yield (entry 6). Because structural tuning is easier for **4** than for *t*BrettPhos, however, we next focused on reaction condition screening using ligand **4**. Substrates containing *N*-SEM and *N*-methoxymethyl (MOM) protecting groups produced comparable yields (entries 6 and 7). Therefore, we used *N*-MOM protected **1b** as a model substrate for optimizing the reaction conditions.

Increasing the catalyst loading from 5 mol% to 20 mol% improved the yield to 33% (entry 8). Screening of the base (entries 8–11) revealed that Cs₂CO₃ afforded a higher yield than CsOAc and CsOPiv, and K₂CO₃ and Cs₂CO₃ were comparable. As a counterion of the palladium salt, OAc and OPiv produced comparable results (entries 9 and 12). Other palladium sources, such as PdBr₂, PdCl₂(PPh₃)₂, and Pd(PPh₃)₄, afforded less satisfactory results (data not shown). Differences

Table 2. Substrate Scope^[a]

1	2			3	
		P	yield [%]		
		3c : CH ₂ C ₆ H ₅	53		
		3d : CH ₂ C ₆ H ₄ -p-CH ₃	59		
		3e : CH ₂ C ₆ H ₄ -p-OCH ₃	58		
				3f : P = CH ₂ C ₆ H ₅ 30%	
		R ²	yield [%]		
		3g : CH ₃	35		
		3h : CH ₃ O	47		
		3i : PhO	52		
		3j : CF ₃	79		
				3m : CH ₃ 40	
				3n : CF ₃ 36	
		R ²	yield [%]		
		3p : H	72		
		3q : CH ₃	85		
		3r : CF ₃	88		
3o : 58% ^[b]				3s : 82%	

[a] General conditions: **1** (0.10 mmol), **2** (0.20 mmol), palladium complex (0.020 mmol), ligand (0.020 mmol), and base (0.20 mmol) were stirred in toluene (0.5 mL) for 24 h under argon. [b] 2-Chloro-3-methylpyridine was used instead of **2**. (Color figure can be accessed in the online version.)

in the phenanthroline ligand structure between bathophenanthroline **4** and phenanthroline **5** significantly affected the product yield, indicating the importance of the phenyl substituent at the 4- and 7-positions of the phenanthroline skeleton (entries 12 and 13). Studies of the effects of substituents on the 4,7-phenyl groups revealed that the introduction of electron-withdrawing groups improved the yield (entries 14 and 15). Thus, using a Pd(OPiv)₂/7 complex in the presence of Cs₂CO₃ as a base afforded **3b** in 50% yield (entry 15). On the other hand, 4,7-phenyl groups bearing an electron donating methoxy group decrease the yield (entry 16).^{26–29)} Use of less reactive 2-chloropyridine than **2a** afforded **3b** in the same yield (entry 17). The yield was further improved to 74%, when 2-iodopyridine was used (entry 18).

The substrate scope of the C–H *N*-heteroarylation was next investigated under the optimized conditions³⁰⁾ (Table 2). For the protecting groups of imidazole substrates, substituted benzyl groups produced a moderate yield (**3c–3e**). Use of 2-iodopyridine, instead of 2-bromopyridine (**2a**), did not improve the yield in those cases. When the methyl group at the C2 position of *N*-benzyl protected imidazole **1c** was changed to an ethyl group, yield decreased to 30% (**3f**) from 53% (**3c**). The effects of a substituent in a different position of the pyridine ring were studied next using 2-bromopyridine derivatives (**3g–3o**). For C2-substituted bromopyridines, an electron-withdrawing

trifluoromethyl group improved the yield to 79% (**3j**). This may be due to the attenuated product inhibition to the catalyst by **3j**, which contains an electron-withdrawing substituent at the C2 position of the pyridine ring. It is also worthy to note that steric hindrance of the pyridine substrate does not significantly influence the yield: product **3o** containing two methyl groups adjacent to the biaryl axis was obtained in 58% yield.³¹⁾ The reaction proceeded in generally high yield using 3-bromopyridines **2p–2r**, suggesting that the reaction proceeds through an oxidative addition of the heteroaryl bromide to palladium species, and not through an addition-elimination pathway. The reaction was also applicable to 5-bromopyrimidine (**2s**), giving product **3s** in 82% yield. This result indicates that the present reaction conditions may be applicable to a range of *N*-heteroaryl groups other than pyridine derivatives. As limitations of the current reaction conditions, both 2,4-disubstituted and 2-monosubstituted imidazoles produced a low yield (<20%). In addition, the reaction between **1b** and phenyl bromide under the current conditions afforded the corresponding 4-phenyl imidazole product in only 30% yield.

In conclusion, we achieved a catalytic C–H *N*-heteroarylation of *N*-protected 2,5-disubstituted imidazoles. A Pd(OPiv)₂/F-bathophen **7** complex was determined to be the optimal catalyst. Based on the development of the direct C–H functionalization method, structural optimization of the aggregation inhibitors of Aβ for the treatment of Alzheimer's disease is ongoing in our laboratory.

Experimental

A mixture of Pd(OPiv)₂ (6 mg, 0.02 mmol), ligand **7** (7 mg, 0.02 mmol), Cs₂CO₃ (65 mg, 0.20 mmol), imidazole **1b** (14 mg, 0.100 mmol), and 2-iodopyridine (41 mg, 0.200 mmol) in toluene (0.5 mL) was stirred at 120°C for 24 h. After completion of the reaction, the reaction mixture was filtered through a celite pad. After concentration of the filtrate, the crude product was purified by column chromatography on silica gel (EtOAc/MeOH = 20 : 1) to give desired product **3b** as brown oil (16 mg, 74% yield).

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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- The observed ligand effects (Table 1, entries 12–16) might be due to stabilization of the transition state for the concerted metalation-deprotonation step in a presumed catalytic cycle.
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- For possible catalytic cycles, see Supplementary Materials.
- In the cases when the yield was moderate, product inhibition is a possible reason. When product **3h** (50 mol%) was premixed to the coupling reaction between **1b** and 2-bromo-6-methoxypyridine (**2h**) under the conditions using Pd(OPiv)₂ (20 mol%), bathophen (**4**: 20 mol%), and Cs₂CO₃ (2.0 equiv) in toluene (0.2 M) for 24 h under argon, only a trace amount (1%) of **3h** was produced.
- When **3o** was premixed in the product inhibition experiment described in ref instead of **3h**, **3h** was obtained in 18% yield. The result suggests that **3o** is a less effective reaction inhibitor than **3h**, and this property of **3o** might be a reason for the high yield of **3o** in the reaction between **1b** and **2o**.