

Direct multiple C–H bond arylation reaction of heteroarenes catalyzed by cationic palladium complex bearing 1,10-phenanthroline†

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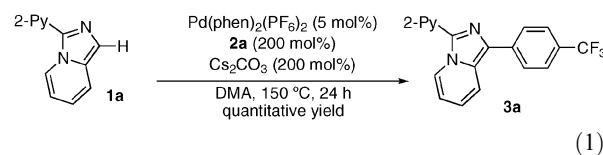
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A cationic palladium complex bearing 1,10-phenanthroline ligand is found to catalyze direct C–H arylation reactions of heteroarenes with aryl iodides to give mono-, di-, or tri-arylated products selectively.

Polyarylated heteroarenes are an important class of compounds that play significant roles as organic materials and bioactive compounds. The preparation of these substances is typically performed by means of transition metal catalyzed cross-coupling of (hetero)aryl metal reagents and (hetero)aryl halides. However, the efficiencies of these reactions remains a troublesome issue.¹ Recently, direct C–H bond functionalization of heteroarenes has received growing attention in the context of streamlined chemical synthesis^{2–7} since it has the potential to serve as an alternative to conventional cross-coupling reactions of heteroarenes. Unfortunately, the repertoire of applicable catalytic systems for these processes remains limited.

In the course of recent studies of the reactions of imidazo[1,5-*a*]pyridines,⁸ we employed a typical Pd-catalyzed C–H bond arylation reaction system^{2c} to carry out arylation of 3-(2-pyridyl)imidazo[1,5-*a*]pyridine (**1a**) at the 1-position. Importantly, conventional cross-coupling catalytic systems do not promote formation of products, a phenomenon that is probably a consequence of inhibition by chelation of the substrate to the catalyst.^{8c} In contrast, reaction of **1a** and 4-trifluoromethylphenyl iodide (**2a**) gives the corresponding arylated product in moderate yield. However, the reaction of 4-methoxyphenylimidazo[1,5-*a*]pyridine (**1b**) with **2a** gives the corresponding product **3b** in a significantly lower yield (Scheme 1). Interestingly, the use of **1a** as an additive in place of PPh₃ in the reaction of **1b** significantly improves the yield of **3b** suggesting that **1a** acts as a good ligand for Pd. Finally, we

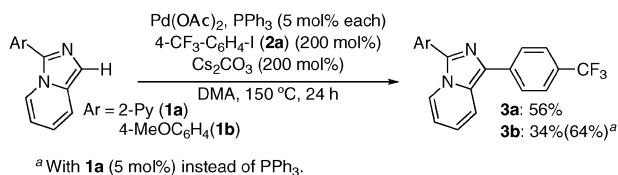
observed that a cationic complex bearing the simple bipyridyl type ligand, Pd(phen)₂(PF₆)₂⁹ (phen = 1,10-phenanthroline), has excellent catalytic activity in the reaction of **1a** to give **3a** quantitatively (eqn (1)).¹⁰



Owing to the unprecedented catalytic activity of such a cationic Pd complex bearing a nitrogen-based ligand, we carried out an investigation exploring catalysis of direct C–H bond arylation reactions of heteroarenes. Below, we describe the results of this effort, which has shown that the novel catalytic system promotes mono-, di-, tri-arylation reactions of heteroarenes leading to arylated products with high degrees of regiocontrol.

To examine the applicability of the Pd(phen)₂(PF₆)₂ catalyst, reactions of benzoxazole (**4**) with several aryl iodides **2** at 150 °C for 20 h and 5 mol% of the catalyst were carried out (Table 1). Iodides **2a–d** undergo Pd(phen)₂(PF₆)₂ promoted coupling reactions with **4** to give the corresponding products **5a–d** in high yields regardless of the nature of the electronic properties of the arene substituents (entries 1–4). The sterically hindered aryl iodides *o*-tolyl iodide (**2e**) and 2,4-dimethylphenyl iodide (**2f**) also participate in coupling processes with **4** to give the respective products **5e–f** with high efficiency (entries 5, 6). Furthermore, heteroaryl iodides, such as 2- and 3-pyridyl (**2g**, **2h**), 2-thienyl (**2i**), and 1-imidazo[1,5-*a*]pyridyl (**2j**) iodides, undergo reactions with **4** to generate the desired products **5g–j** in good to excellent yields (entries 7–10). Reaction of 2,5-diiodothiophene (**2k**) with **4** gives the bis-coupling product **5k** in 89% yield (entry 11). Notably, kinetic plots show that the reaction of high concentrations (1 M) of **4** and **2a** is complete within 40 min at 150 °C.¹⁰ Furthermore, this reaction proceeds even at 70 °C to give **5a** in 49% yield after 20 h.¹⁰ Finally, the cationic palladium complex Pd(phen)₂(PF₆)₂ is stable in moist air and, as a result, reactions can be performed on a bench-top without using Schlenk techniques.

The catalyst Pd(phen)₂(PF₆)₂ can be used to promote direct C–H bond arylation reactions of a wide variety of heteroarenes. For example, benzothiazole (**6**) undergoes coupling with iodides **2a–c** to give the corresponding products **7a–c** in excellent yields (Table 2, entries 1–3). Caffeine (**8**) also participates in a reaction with **2a** to give the adduct **9** in high yield (entry 4). Finally, reaction of *N*-methylindole (**10**) and **2a**



Scheme 1 Reaction of imidazo[1,5-*a*]pyridines and trifluoromethylphenyl iodide.

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Table 1 Reaction of benzoxazole and aryl iodides^a

Entry	I-Ar (2)	Product	Yield (%)
1			5a: 94%
2			5b: >99%
3			5c: 89%
4			5d: 82%
5			5e: 82%
6			5f: 84%
7			5g: 83%
8			5h: 82%
9			5i: 81%
10			5j: >99%
11 ^b			5k: 89%

^a Reactions were carried out with **4** (0.5 mmol) and aryl iodide (110 mol%) in the presence of Pd(phen)₂(PF₆)₂ (5 mol%) and Cs₂CO₃ (110 mol%) in DMA at 150 °C for 20 h. ^b 55 mol% of Ar-I was used.

takes place in a regioselective fashion at the indole 1-position to give **11** in quantitative yield (entry 5).

The catalytic system was found to be useful for carrying out multiple arylation reactions of heteroarenes. For example, thiophene reacts with 2 equiv. of **2a** in the presence of Pd(phen)₂(PF₆)₂ to give the 2,5-arylated product **12** exclusively in 80% yield on a 0.5 mmol scale (on a gram scale the

Table 2 Reaction between several heteroarenes and aryl iodides^a

Entry	Ar-H	I-Ar' (2)	Ar-Ar'	Yield (%)
1		2a		7a: 86%
2		2b		7b: 95%
3		2c		7c: 100%
4		2a		9: 82%
5		2a		11: 84%

^a Reactions were carried out using a heteroarene (0.5 mmol) and aryl iodide (110 mol%) in the presence of Pd(phen)₂(PF₆)₂ (5 mol%) and Cs₂CO₃ (110 mol%) in DMA at 150 °C for 20 h.

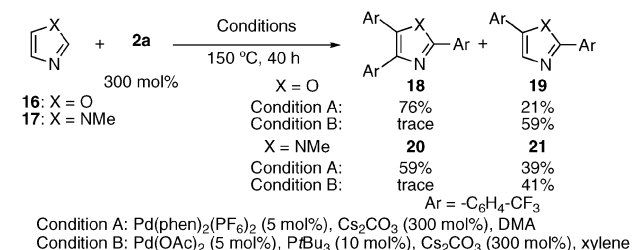
Table 3 Bis-arylation reactions of heteroarenes^a

Entry	Product	Result
1		12 18 h, 80%
2		20 h, 11% ^b
3		13 20 h, 78%
4		14 12 h, 79%
5		15 20 h, 51%

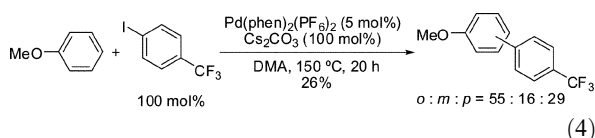
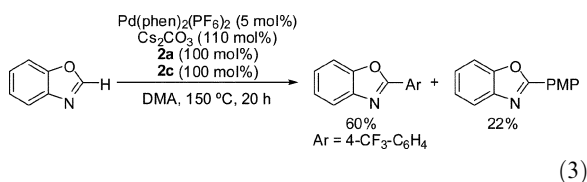
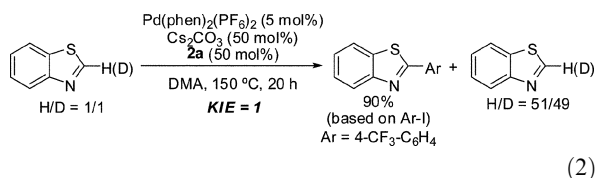
^a Reactions were carried out using a heteroarene (0.5 mmol) and aryl iodide (110 mol%) in the presence of Pd(phen)₂(PF₆)₂ (5 mol%) and Cs₂CO₃ (110 mol%) in DMA at 150 °C for 20 h. ^b Pd(OAc)₂ (5 mol%) and PrBu₃ (10 mol%) were used instead of Pd(phen)₂(PF₆)₂.

yield is 84%) (Table 3, entry 1).¹¹ In contrast, the reaction performed using the Pd-phosphine system^{2a} affords **12** in only 11% yield (entry 2). Sterically hindered 3-methylthiophene also couples with **2a** at the 2- and 5-positions in high yield (entry 3). In addition, reaction of *N*-methylpyrrole takes place with a similar selectivity to that of thiophene to afford the bis-arylated product **14** in high yield (entry 4). Importantly, this straightforward and selective diarylation reaction of unsubstituted thiophene and *N*-methylpyrrole has only rarely been observed.^{2a,b} Lastly, diarylation of benzofuran with 2 equiv. of **2a** takes place to afford a 2,3-aryl substituted benzofuran **15** (entry 5).

We have also observed that the cationic Pd complex Pd(phen)₂(PF₆)₂ catalyzes triarylation reactions of the simple heterocycles, oxazole (**16**) and *N*-methylimidazole (**17**). In reactions of these substances with iodide **2a** which produce **18** and **20**, respectively, all of the arene hydrogens are substituted by aryl groups (Scheme 2). The processes are accompanied by formation of minor amounts of the corresponding diarylated products **19** and **21**. The observations are in marked contrast to those made in studies of the related Pd-phosphine catalyzed reactions of **16** and **17** (Condition B), where **19** and **21** are the sole products generated. The processes described above are the first examples of triarylation reactions occurring by direct C-H arylation of simple heteroarenes.^{2a}

**Scheme 2** Triple arylation of heteroarenes.

Although the mechanism of the catalytic process described above is not yet clear, several observations were made that provide insight into the mode of action of $\text{Pd}(\text{phen})_2(\text{PF}_6)_2$. The results of an intermolecular competitive reaction of deuterium-labeled **6** ($\text{H}/\text{D} = 1/1$) with **2a** gives a KIE value of unity (eqn (2)). This finding clearly suggests that elimination of hydrogen from the heteroarene is not involved in the rate-limiting step. The results of a competitive reaction of **4** with an equimolar ratio of **2a** and **2c** demonstrate that the electron deficient aryl halide **2a** undergoes coupling faster than its electron rich counterpart **2c** (eqn (3)). This observation suggests that either oxidative addition of the aryl iodide to the Pd catalyst or electrophilic addition of the resulting Pd complex to the heteroarene is rate-limiting provided that the reaction is taking place *via* a conventional pathway. Alternatively, the $\text{Pd}(\text{phen})_2(\text{PF}_6)_2$ catalyzed coupling reaction might follow a radical mechanism. Recently, an Ir-catalyzed reaction of anisole with iodobenzene was reported to give three regioisomeric monoarylated products with an unusually high *ortho* selectivity ($o:m:p = 72:16:12$). The intermediacy of a phenyl radical in this process has been proposed.¹² Interestingly, a similar *ortho* selectivity was observed in $\text{Pd}(\text{phen})_2(\text{PF}_6)_2$ promoted arylation reaction of anisole with **2a** (eqn (4)).



In conclusion, the investigation described above has demonstrated that the palladium complex bearing a nitrogen-based ligand, $\text{Pd}(\text{phen})_2(\text{PF}_6)_2$, promotes efficient direct C–H bond arylation reactions of heteroarenes. This catalytic system can be used to carry out highly selective multiple arylation reactions of unsubstituted heteroarenes. Further mechanistic studies of this process and its application to the synthesis of functional materials are currently underway.

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