

Palladium(II)-Catalyzed Oxidative C–H/C–H Cross-Coupling of Heteroarenes

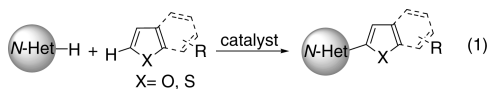
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The structural motif with heteroaryl–heteroaryl bonds is a predominant substructure of many natural products, pharmaceuticals, and electronic materials. Conventional wisdom states that these carbon–carbon biheteroaryl linkages are forged via transition metal catalyzed cross-coupling of a heteroaryl halide or pseudohalide with a heteroaryl organometallic reagent.¹ However, preactivation of heteroaromatic carbon fragments with metal-containing functionalities and halides may involve several synthetic steps. In particular, some important types of heteroaryl organometallic compounds have proven challenging to synthesize and may even be inadequately stable to participate in the cross-coupling process. Thus, catalytic oxidative C–H/C–H cross-coupling of two heteroarenes would be the most ideal strategy to solve the problems (Figure 1, C).

Transition metal catalyzed direct (hetero)arylation of (hetero)arenes has emerged and continues to attract worldwide interest, in which one of two coupling partners, mostly the more troublesome (hetero)aryl organometallic species, is substituted with a simple (hetero)arene itself.² Quite recently, Fagnou and co-workers made a significant breakthrough in the Pd(II)-catalyzed oxidative cross-coupling of unactivated heteroarenes through 2-fold C–H activation (Figure 1, B).^{3–5} However, the metal-catalyzed oxidative cross-coupling of two heteroaryl C–H bonds to form unsymmetrical biheteroaryl molecules remains a daunting hindrance (Figure 1, C).⁶ Herein, we wish to explore the Pd(II)-catalyzed C–H/C–H cross-coupling of various *N*-containing heteroarenes (e.g., azoles, and pyridine *N*-oxides) with π -electron-excessive five-membered heterocycles (e.g., thiophenes, and furans) (eq 1). We envisioned whether the distinctly differential π -electronic characteristics between the two types of heteroarenes would facilitate an inversion/selectivity in the two metalation steps of the catalytic cycle.^{5a} However, we may face a formidable challenge as such electron-rich five-membered heteroarenes are susceptible to oxidative homocoupling in the presence of Pd(II) salts (Figure 1, A).⁷ In this study, we describe the discovery, development, and solution of reactions that meet these challenges.



Xanthines are important biologically active alkaloids. 8-Heteroaryl-substituted xanthines are highly potent antagonists at human A_{2B} adenosine receptors.⁸ Following our continuing interest in the direct C-arylation of xanthines,⁹ we initially focused on the cross-coupling of caffeine with 2-formylthiophene with Pd(OAc)₂ (Table S1). After screening several parameters (e.g., solvent, oxidant, additive, and temperature), a catalytic system comprising Pd(OAc)₂ as catalyst, Cu(OAc)₂·H₂O as oxidant, pyridine, and 1,4-dioxane proved to be efficient. Gratifyingly, the heteroarylation could occur

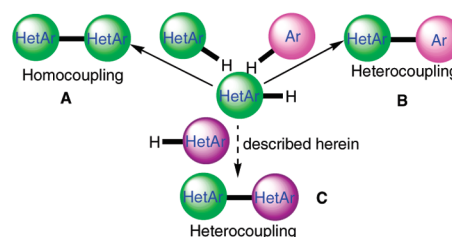
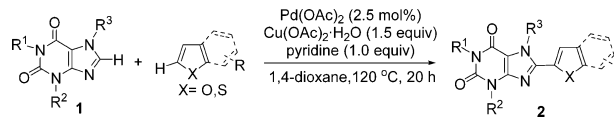


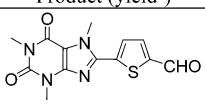
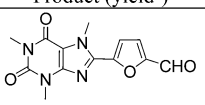
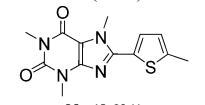
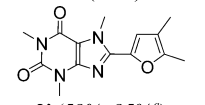
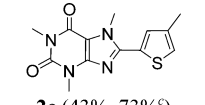
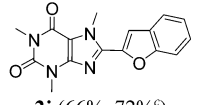
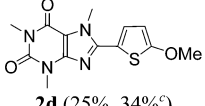
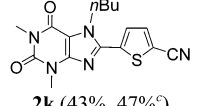
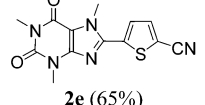
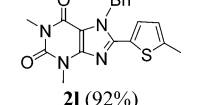
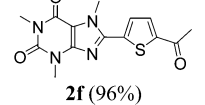
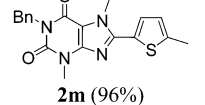
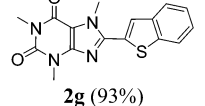
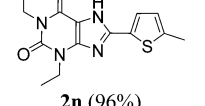
Figure 1. Evolution of transition metal catalyzed oxidative (hetero)arylation of heteroarenes via double C–H activation.

with a low catalyst loading of 2.5 mol % of Pd(OAc)₂ to afford 93% yield of **2a** with complete regioselectivity (Table 1, entry 1). An X-ray analysis of single crystals **2a** confirmed that a direct C–H/C–H cross-coupling took place between C-5 on 2-formylthiophene and C-8 on caffeine (Figure S1a).

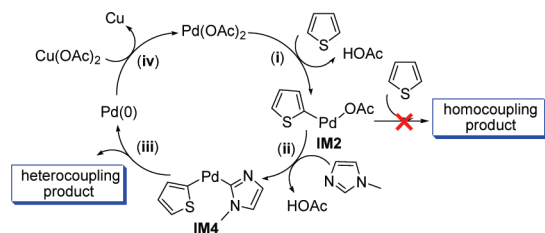
Subsequently, a variety of thiophenes and furans were tested with xanthines (e.g., caffeine, *n*-butyl theophylline, benzylic theophylline, benzylic theobromine, and 1,3-diethyl xanthine) (Table 1). These results demonstrated that thiophenes and furans with a relatively broad range of substituents afforded good to excellent yields. Worthy of note was that the reaction of benzothiophene or benzofuran with caffeine exclusively gave rise to the heteroarylated products at the 2-position of benzothiophene and benzofuran in 93% and 66% yields, respectively (Table 1, entries 7 and 10). Interestingly, the reaction of free (NH)-1,3-diethyl xanthine proceeded well (Table 1, entry 14).

Although more detailed investigations of the reaction mechanism are currently underway, in combination with the DFT calculation based on the coupling of *N*-methylimidazole and thiophene, we proposed a plausible catalytic cycle illustrated in Figure 2 (for the detailed DFT calculation, see Supporting Information). In the first metalation step, the DFT calculation suggested that the abstraction of hydrogen from thiophene should easily take place in the reaction system. Thus, thiophene would undertake a regioselective electrophilic C–H substitution (S_EAr) of Pd(OAc)₂ to generate α -thienylpalladium(II) intermediate **IM2** (Figure 3).^{7a} In the second metalation step, although the calculation showed that dithiophene might be generated from **IM2** via the electrophilic transition state **Side-TS** (Figure 3b), as compared to the intermediate **IM3** related to the heterocoupling (Figure 3a), the intermediate **Side-IM3** related to the homocoupling might be an unstable complex because its relative energy is higher than **IM2**. Therefore, when catalyst, thiophene, and *N*-methylimidazole coexist in the reaction system, **IM3** might be the predominant intermediate after the formation of **IM2**. It demonstrated that the catalytic system inverted its selectivity in the crucial metalation step to react with the other heteroarene. Subsequently, **IM3** would go through the concerted metalation–

Table 1. Scope of Oxidative Cross-Coupling of Xanthenes with a Variety of Thiophenes or Furans^a


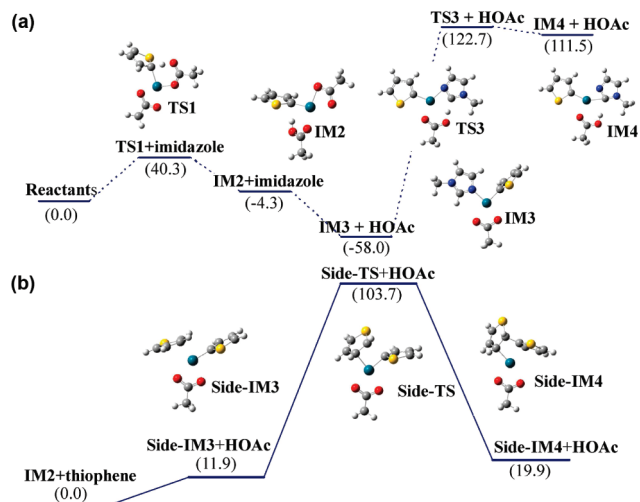
Entry	Product (yield ^b)	Entry	Product (yield ^b)
1	 2a (93%)	8	 2h (85%)
2	 2b (96%)	9	 2i (59%, 95% ^c)
3	 2c (43%, 73% ^c)	10	 2j (66%, 72% ^c)
4	 2d (25%, 34% ^c)	11	 2k (43%, 47% ^c)
5	 2e (65%)	12	 2l (92%)
6	 2f (96%)	13	 2m (96%)
7	 2g (93%)	14	 2n (96%)

^a Reaction conditions: **1** (0.5 mmol), thiophenes or furans (3 equiv), Pd(OAc)₂ (2.5 mol %), Cu(OAc)₂·H₂O (1.5 equiv), pyridine (1.0 equiv), and 1,4-dioxane (0.6 mL) at 120 °C for 20 h. ^b Isolated yield based on **1**. ^c CuCl (10 mol %) as additive.

**Figure 2.** Plausible catalytic cycle of oxidative C–H/C–H cross-coupling of heteroarenes.

deprotonation (CMD) process to form the key heterocoupling intermediate **IM4**, which might be rate-determining in the entire reaction.¹⁰

Considering that Cu(I) salts have been extensively used as catalyst or activator in direct C-arylation of *N*-heteroarenes,^{9a,11} we speculated whether an additional introduction of substoichiometric Cu(I) salt into this catalytic system could assist the C–H bond activation of *N*-heteroarenes. As expected, a catalytic amount of CuCl significantly improved catalytic efficiency and regioselectivity (Table 1, entries 3–4, 9–11).

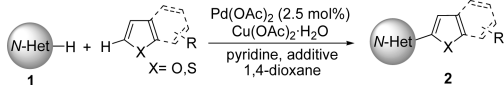
**Figure 3.** Energy profiles of (a) the heterocoupling of *N*-methylimidazole and thiophene and (b) the homocoupling to dithiophene from **IM2** calculated at the B3LYP/6-311++G(2d,2p), SDD level. Relative energies in kJ/mol are listed in parentheses. Color code: C (gray), N (blue), O (red), S (yellow), Pd (cyan), and H (white). Also see Figures S2 and S3.

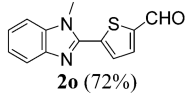
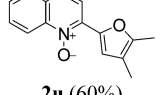
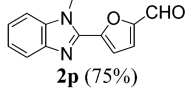
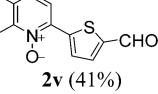
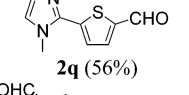
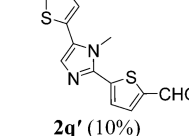
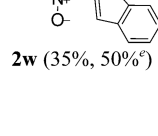
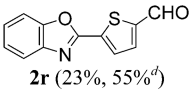
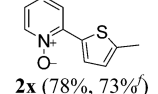
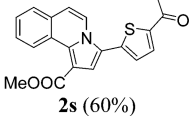
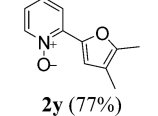
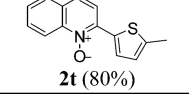
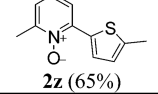
To further expand the scope of methodology, the cross-coupling of other *N*-heteroaromatic substrates with various furans or thiophenes were investigated (Table 2). It was gratifying to find that *N*-methylbenzimidazole was heteroarylated with 2-formylthiophene or 2-formylfuran in satisfactory yields (Table 2, entries 1–2). Notably, the reaction of *N*-methylimidazole with 2-formylthiophene gave 2-substituted *N*-methylimidazole **2q** as a major product (56%) together with a small amount of 2,5-disubstituted *N*-methylimidazole **2q'** (10%) (Table 2, entry 3).¹² The structure of **2q** was confirmed by an X-ray analysis (Figure S1b). In contrast, the reaction of benzoxazole with 2-formylthiophene gave a low yield of heterocoupling product (23%). Fortunately, addition of 20 mol % of CuCl and 20 mol % of 1,10-phenanthroline dramatically improved the heterocoupling up to 55% yield (Table 2, entry 4). In addition to the above-mentioned π -electron-rich azoles, 3-unsubstituted indolizine could also couple with 2-acetylthiophene to furnish **2s** in 60% yield (Table 2, entry 5).

To our delight, our synthetic strategy was also suitable for π -electron-poor *N*-heteroarene *N*-oxides while CuBr (10 mol %) was used as additive.^{5d} For example, quinoline and pyridine *N*-oxides were monoheteroarylated with 2-methylthiophene, 2,3-dimethylfuran, 2-formylthiophene, or benzothiophene to afford the corresponding heterocoupling products in moderate to good yields (Table 2, entries 6–12). In addition, it is noteworthy that the synthesis of 2-(5-methylthiophen-2-yl)-quinoline *N*-oxide (**2t**) was performed without problems on an ~2 g scale, which should represent a potential bench-scale preparation.

Although these examples used up to 3–4 equiv of one of the coupling components, the reactions were indeed reasonably selective for the cross-coupled products as opposed to the statistical distribution of products. For example, the reactions of 2-formylthiophene with various azoles gave the homocoupling yields of 2-formylthiophene in a range of ~10% as the reactions arising from benzothiophene afforded a negligible amount of unwanted bibenzothiophene.

In summary, we have developed for the first time the low catalyst loading, highly efficient and regioselective Pd(II)-catalyzed oxidative cross-coupling of heteroaromatic compounds via 2-fold C–H activation. The use of substoichiometric Cu(I) as an activator has been found to induce enhanced reactivity in reactions with azoles

Table 2. Scope of Oxidative Cross-Coupling of *N*-Heteroarenes with a Variety of Thiophenes or Furans


Entry	Product (yield ^c)	Entry	Product (yield ^c)
1 ^a	 2o (72%)	7 ^b	 2u (60%)
2 ^a	 2p (75%)	8 ^b	 2v (41%)
	 2q (56%)		
3 ^a	 2q' (10%)	9 ^b	 2w (35%, 50% ^c)
4 ^a	 2r (23%, 55% ^d)	10 ^b	 2x (78%, 73% ^d)
5 ^a	 2s (60%)	11 ^b	 2y (77%)
6 ^b	 2t (80%)	12 ^b	 2z (65%)

^a Reaction conditions: **1** (0.5 mmol), thiophenes or furans (3 equiv), Pd(OAc)₂ (2.5 mol %), Cu(OAc)₂·H₂O (1.5 equiv), and pyridine (1.0 equiv) in 1,4-dioxane (0.6 mL) at 120 °C for 20 h. ^b Reaction conditions: thiophenes or furans (0.5 mmol), **1** (4 equiv), Pd(OAc)₂ (2.5 mol %), CuBr (10 mol %), Cu(OAc)₂·H₂O (1.5 equiv), and pyridine (1.0 equiv) in 1,4-dioxane (1.2 mL) at 110 °C for 30 h. ^c Isolated yield based on **1** (entries 1–5), thiophenes or furans (entries 6–12). ^d CuCl (20 mol %), 1,10-phenanthroline (20 mol %), and *N,N*-dimethylacetamide (DMA) as solvent. ^e Carried out at 120 °C. ^f Pyridine *N*-oxide (3 equiv).

and pyridine *N*-oxides. This catalytic system allows the C–H/C–H heterocoupling of not only electron-rich *N*-containing heteroarenes (e.g., xanthenes, azoles, and indolizines) but also electron-poor pyridine *N*-oxides with diverse thiophenes or furans. We anticipate that this finding may have a broader impact on the synthesis of unsymmetrical biheteroaryl molecules in medical, material, and natural product chemistry and have more potential industrial use.

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Supporting Information Available: Data and copies of ¹H and ¹³C NMR and HRMS spectra for all new compounds, two CIF files, ORTEP diagrams of **2a** and **2b**, experimental procedures, and computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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