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Oxygen as an oxidant in palladium/copper-cocatalyzed oxidative C–H/C–H cross-coupling between two heteroarenes

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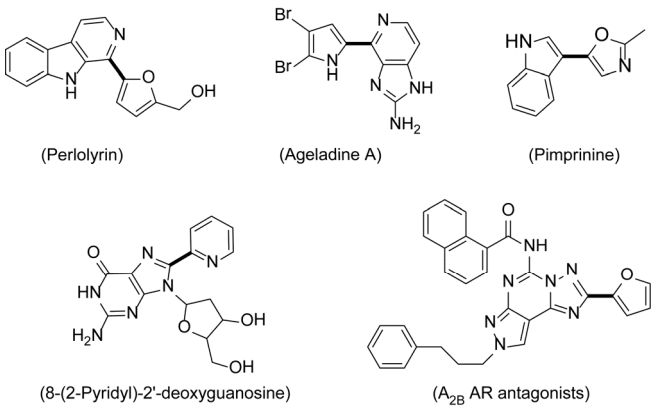
The palladium/copper-cocatalyzed oxidative C–H/C–H cross-coupling between two heteroarenes by using molecular oxygen as an oxidant instead of metal oxidants has been developed for the first time to construct biheteroaryl motifs. A relatively broad range of thiophenes, furans and indoles can smoothly couple with various *N*-heteroarenes in satisfactory yields. This catalytic system with O_2 as the terminal oxidant offers clear advantages of economically feasible and eco-friendly processes.

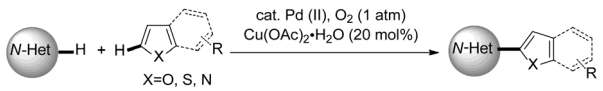
biheteroaryl, molecular oxygen, C–H/C–H cross-coupling, green chemistry

1 Introduction

The biheteroaryl structural motif is ubiquitous in various natural products, pharmaceuticals and organic functional materials (Scheme 1) [1]. From the viewpoint of synthetic simplicity and atom economy, transition metal-catalyzed oxidative C–H/C–H cross-coupling reactions between two heteroarenes are undoubtedly one of the most ideal strategies to forge heteroaryl-heteroaryl linkages [2]. However, these reactions often require stoichiometric amounts of silver (I), or copper (II) salts as oxidants. Employing atmospheric oxygen or molecular oxygen as an oxidant would clearly make them more economic, practical and environmentally-friendly. Over the past decade, considerable attentions have been focused on various oxidative coupling reactions by using oxygen as an oxidant [3]. However, oxygen as an oxidant in transition metal-catalyzed oxidative C–H/C–H cross-coupling between two different heteroarenes remains unexplored. Herein, we report an efficient palladium/copper-cocatalyzed oxidative C–H/C–H cross-coupling of thiophenes, furans and indoles with *N*-heteroarenes by using molecular oxygen as an oxidant to deliver biheteroaryl structures (Scheme 2).



Scheme 1 Selected medicinal and natural molecules containing biheteroaryl structural motif.



Scheme 2 Palladium/copper-cocatalyzed oxidative C–H/C–H cross-coupling of thiophenes, furans and indoles with heteroarenes by using O_2 as an oxidant.

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2 Experimental

2.1 General methods

NMR spectra were obtained on a Bruker AMX-400 (Switzerland) or a Varian Inova 400 spectrometer. The ^{1}H NMR (400 MHz) chemical shifts were measured based on $CDCl_3$ or DMSO-d_6 or TMS as the internal reference ($CDCl_3$, δ=7.26 ppm; DMSO-d_6, δ=2.50 ppm; TMS, δ=0.00 ppm). The ^{13}C NMR (100 MHz) chemical shifts were given using $CDCl_3$ or DMSO-d_6 as the internal standard. High-resolution mass spectra (HR-MS) were obtained with a Waters-Q-TOF-Premier (ESI, U.K.). Unless otherwise noted, all reagents were commercially available and used without further purification.

2.2 Optimization of the oxidative C–H/C–H cross-coupling between two heteroarenes by using O_2 as the terminal oxidant

A flame-dried Schlenk test tube with a magnetic stirring bar was charged with Pd catalyst (0.0125 mmol, 2.5 mol%), additive, caffeine (**1a**, 97 mg, 0.5 mmol), pyridine (0.5 mmol, 1.0 equiv.) and 1,4-dioxane (1.0 mL). After the reaction mixture was stirred for 10 min at room temperature, 2-formylthiophene (**2a**, 168.2 mg, 1.5 mmol, 3.0 equiv.) was added. The resulting mixture was heated at 140 °C for 30 h under 1 atm of oxygen or air, and then cooled to ambient temperature. The mixture was diluted with 30 mL of CH_2Cl_2, filtered through a celite pad, and then washed with 10–20 mL of CH_2Cl_2. The combined organic extracts were concentrated and the resulting residue was purified by column chromatography on silica gel (CH_2Cl_2/acetone=14:1, *v*/*v*) to provide 1,3,7-trimethyl-8-(5-formylthiophen-2-yl)-xanthine (**3a**) as a yellow solid.

2.3 General procedure for the oxidative C–H/C–H cross-coupling of thiophenes and furans with *N*-heteroarenes using O_2 as the terminal oxidant

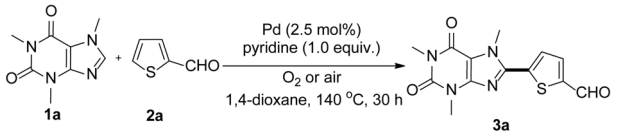
A flame-dried Schlenk test tube with a magnetic stirring bar was charged with Pd(dppf)Cl_2 (0.0125 mmol, 2.5 mol%), $Cu(OAc)_2\cdot H_2O$ (0.1 mmol, 0.2 equiv.), *N*-heteroarene (**1**, 0.5 mmol), pyridine (0.5 mmol, 1.0 equiv.) and 1,4-dioxane (1.0 mL). After the reaction mixture was stirred for 10 min at room temperature, thiophene, furan or indole (**2**, 1.5 mmol, 3.0 equiv.) was added. The resulting mixture was heated at 140 °C for 30 h under 1 atm of oxygen, and then cooled to ambient temperature. The mixture was diluted with 30 mL of CH_2Cl_2, filtered through a celite pad, and then washed with 10–20 mL of CH_2Cl_2. The combined organic extracts were concentrated and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

3 Results and discussion

Xanthine (3,7-dihydro-purine-2,6-dione) is a kind of purine bases found in most human body tissues and fluids and in other organisms [4]. 8-Heteroaryl-substituted xanthines are potent antagonists at human A_{2B} adenosine receptors [5]. Therefore, the oxidative C–H/C–H cross-coupling of thiophenes and furans with xanthines (e.g., caffeine, theophylline, and theobromine) to prepare 8-heteroaryl-substituted xanthines was first investigated. Based on our recent research progresses in oxidative C–H/C–H cross-coupling [6], caffeine (**1a**) and 2-formylthiophene (**2a**) were chosen as model substrates to optimize the reaction condition (Table 1). Gratifyingly, the biheteroaryl **3a** was obtained in 33% yield by using O_2 as the oxidant (Entry 1). It is known that copper salts have been used as catalyst or activator in direct C–H arylation of *N*-heteroarenes. The addition of 20 mol% of $Cu(OAc)_2\cdot H_2O$ as an additive significantly improved the yield from 33% to 71% (Entry 2). The reduction of the amount of $Cu(OAc)_2\cdot H_2O$ resulted in a decreased yield of 58% (Entry 3). We rationalized that a relatively acidic C2–H bond of azole might undergo C–H cupration with $Cu(OAc)_2$ and subsequent transmetalation with the heteroaryl-PdL_n species to form the key heterocoupling intermediate heteroaryl-Pd-azole complex [6a–6c]. After screening several palladium catalysts, Pd(dppf)Cl_2 proved to be superior to $Pd(OAc)_2$, $Pd(MeCN)_2Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(acac)_2$, and $Pd(PPh_3)_4$, which improved the coupling yield to 95% (Entries 4–9). It should be noted that the reaction even smoothly underwent in 83% yield under air (Entry 10). Finally, the catalytic system composed of Pd(dppf)Cl_2 (2.5 mol%) and pyridine (1.0 equiv.) gave the best result (95% yield) in the presence of 1 atm of O_2 as the terminal oxidant and 20 mol% of $Cu(OAc)_2\cdot H_2O$ as a cocatalyst in 1,4-dioxane at 140 °C for 30 h.

With the optimized conditions in hand, we next explored the scope of the methodology with respect to the π-electron-rich heteroarenes. As summarized in Table 2, a wide array of π-electron-rich heteroarenes (e.g., thiophenes, furans, indoles, benzothiophenes and benzofurans) smoothly coupled with caffeine to give the desired biheteroaryl products in moderate to excellent yields (**3a–3k**). No matter heteroarenes contain an electron-donating or electron-withdrawing group, all of them could be well converted to the desired products. A variety of functional groups such as aldehyde, methoxyl, acetyl and cyan could be highly tolerated under the reaction conditions. To our delight, 2-methoxylthiophene, which exhibited a low reactivity by using stoichiometric amounts of $Cu(OAc)_2\cdot H_2O$ in our previously reported catalytic system [6a], could proceed well under our catalytic system with O_2 as the terminal oxidant (**3c**). Worthy of note was that the coupling reaction occurred at the sterically less hindered C5-position when 3-methylthiophene was used as a coupling partner (**3d**).

Table 1 Optimization of the oxidative C–H/C–H cross-coupling of **1a** with **2a** by using O_2 as the terminal oxidant [a)]

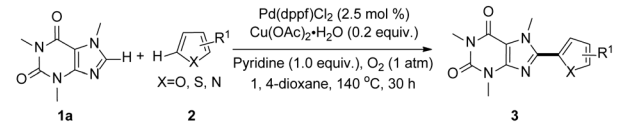


1a **2a** **3a**

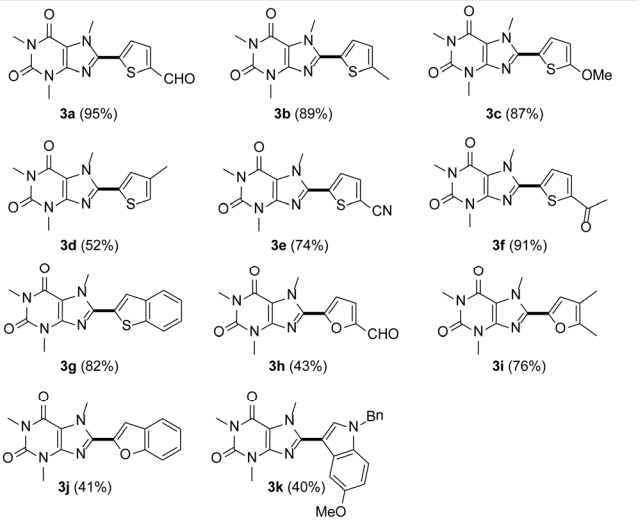
Entry	Pd source	Addtive (equiv.)	Yield (%) [b)]
1	$Pd(OAc)_2$	–	33
2	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$ (0.2)	71
3	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$ (0.1)	58
4	$Pd(MeCN)_2Cl_2$	$Cu(OAc)_2 \cdot H_2O$ (0.2)	53
5	$Pd(PhCN)_2Cl_2$	$Cu(OAc)_2 \cdot H_2O$ (0.2)	54
6	$Pd(PPh_3)_2Cl_2$	$Cu(OAc)_2 \cdot H_2O$ (0.2)	63
7	$Pd(acac)_2$	$Cu(OAc)_2 \cdot H_2O$ (0.2)	86
8	$Pd(dppf)Cl_2$	$Cu(OAc)_2 \cdot H_2O$ (0.2)	95
9	$Pd(PPh_3)_4$	$Cu(OAc)_2 \cdot H_2O$ (0.2)	82
10 [c)]	$Pd(dppf)Cl_2$	$Cu(OAc)_2 \cdot H_2O$ (0.2)	83
11 [d)]	$Pd(dppf)Cl_2$	$Cu(OAc)_2 \cdot H_2O$ (0.2)	82
12	$Pd(dppf)Cl_2$	$Cu(OAc)_2 \cdot H_2O$ (0.1)	84
13 [e)]	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$ (0.2)	72

a) Reaction conditions: caffeine (**1a**, 0.5 mmol), 2-formylthiophene (**2a**, 3.0 equiv.), Pd source (2.5 mol%), additive, and pyridine (1.0 equiv.) in 1,4-dioxane (1.0 mL) at 140 °C for 30 h under 1 atm of O_2 or air; b) isolated yield based on caffeine; c) under air; d) the reaction was carried out at 130 °C; e) dppf (2.5 mol%) was added.

Table 2 Scope of oxidative C–H/C–H cross-coupling of caffeine with a variety of thiophenes or furans or indole [a, b)]



1a **2** **3**

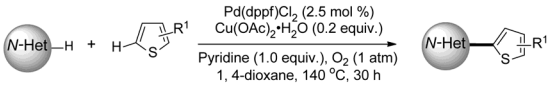


a) Reaction conditions: caffeine (**1a**, 0.5 mmol), thiophene, furan or indole (**2**, 3.0 equiv.), $Pd(dppf)Cl_2$ (2.5 mol%), $Cu(OAc)_2 \cdot H_2O$ (0.2 equiv.), and pyridine (1.0 equiv.) in 1,4-dioxane (1.0 mL) at 140 °C for 30 h under 1 atm of O_2; b) isolated yield based on caffeine after column chromatography.

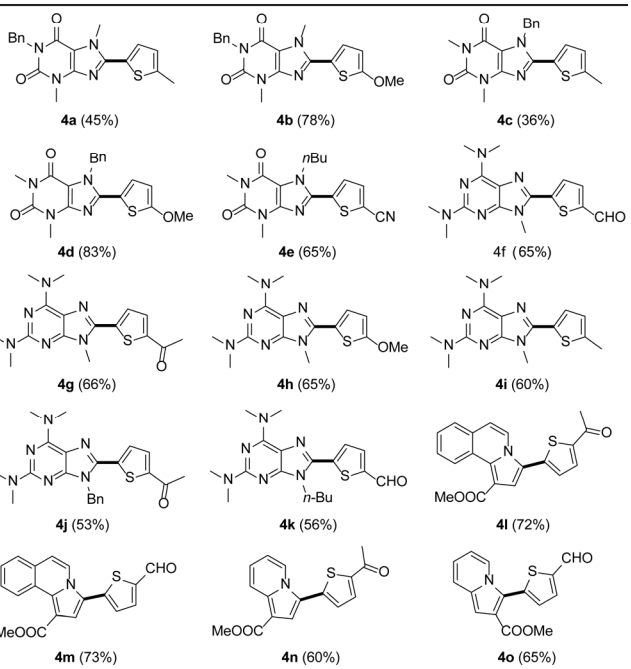
To further expand the scope of methodology, we applied this protocol to other *N*-heteroarenes for the synthesis of biheteroarenes (Table 3). Purines as "functional" π-components are prevalent in organic functional molecules with biological relevance [7]. Recently, direct arylation of purines has attracted a growing number of attentions [8]. To our delight, various purine derivatives could couple with a series of thiophenes in satisfactory yields under O_2 atmosphere (**4a**–**4k**). Dimethylamino, widely used as a functional group in organic functional materials, was also well tolerated under the current catalytic system. The (hetero)aryl indolizine units are a type of important components of natural products, fluorescent materials and bioactive molecules [9]. Our protocol was also suitable for the synthesis of thiophenyl-substituted indolizines (**4l**–**4o**).

Biheteroaryls containing pyridines and related azines are frequently found in natural products, pharmaceuticals, and functional synthetic materials [10]. One of the most effective methods for the construction of these biheteroaryl linkages would be the direct C–H (hetero)arylation of electron-poor *N*-heteroarene *N*-oxides due to the high reactivity of C–H bond adjacent to the nitrogen atom [11]. It was

Table 3 Scope of oxidative C–H/C–H cross-coupling of *N*-heteroarenes with a variety of thiophenes [a, b)]

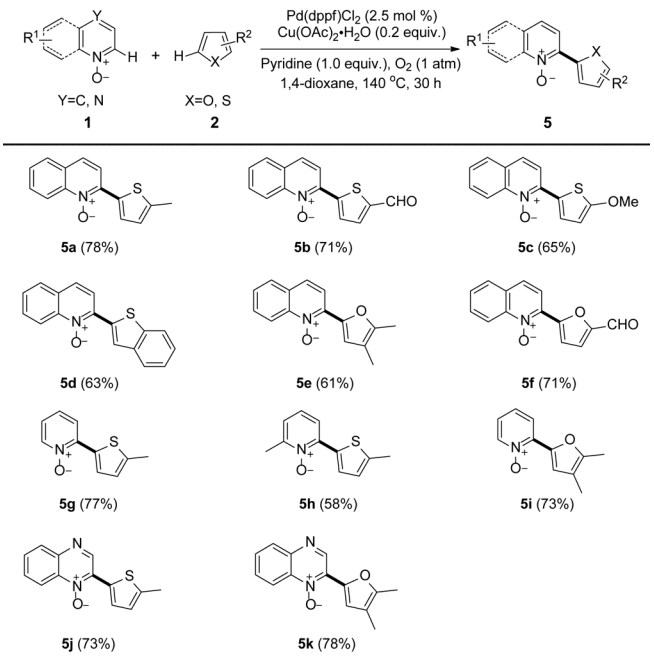


1 **2** **4**



a) Reaction conditions: *N*-heteroarene (**1**, 0.5 mmol), thiophene or furan (**2**, 3.0 equiv.), $Pd(dppf)Cl_2$ (2.5 mol%), $Cu(OAc)_2 \cdot H_2O$ (0.2 equiv.), and pyridine (1.0 equiv.) in 1,4-dioxane (1.0 mL) at 140 °C for 30 h under 1 atm of O_2; b) isolated yield based on *N*-heteroarene after column chromatography.

Table 4 Scope of oxidative C–H/C–H cross-coupling of *N*-heteroarene *N*-oxides with a variety of thiophenes or furans [a, b]



a) Reaction conditions: *N*-heteroarene *N*-oxide (**1**, 0.5 mmol), thiophene or furan (**2**, 3.0 equiv.), $Pd(dppf)Cl_2$ (2.5 mol%), $Cu(OAc)_2 \cdot H_2O$ (0.2 equiv.), and pyridine (1.0 equiv.) in 1,4-dioxane (1.0 mL) at 140 °C for 30 h under 1 atm of O_2; b) isolated yield based on *N*-heteroarene *N*-oxide after column chromatography.

delightful that our catalytic system with O_2 as the terminal oxidant could also effectively promote the cross-coupling of various *N*-heteroarene *N*-oxides (e.g., pyridine *N*-oxide, quinoline *N*-oxide, and quinoxaline *N*-oxide) with thiophenes or furans at the C2 position of *N*-heteroarene *N*-oxides (Table 4). It was noteworthy that the synthesis of 2-(5-methylthiophen-2-yl)-quinoline *N*-oxide (**5a**) could be performed without problems on gram scale (~2 g), which avoided the use of stoichiometric amounts of metal oxidant and should represent a potential bench-scale preparation.

4 Conclusions

In summary, we have developed a Pd(II)/copper-cocatalyzed oxidative C–H/C–H cross-coupling of π-electron-rich five-membered heterocycles (e.g., thiophenes, furans, indoles, benzothiophenes and benzofurans) with various *N*-containing heteroarenes (e.g., purines, indolizines and *N*-heteroarenes *N*-oxides) by using molecular oxygen as the terminal oxidant. A variety of functional groups are well tolerated under the catalytic system. We anticipate that this facile and efficient process may be emerged as a powerful tool for the construction of unsymmetrical biheteroaryls in medical, material, and natural product chemistry.

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