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Palladium(II)-Catalyzed Oxidative C–H/C–H Cross-Coupling between Two Structurally Similar Azoles

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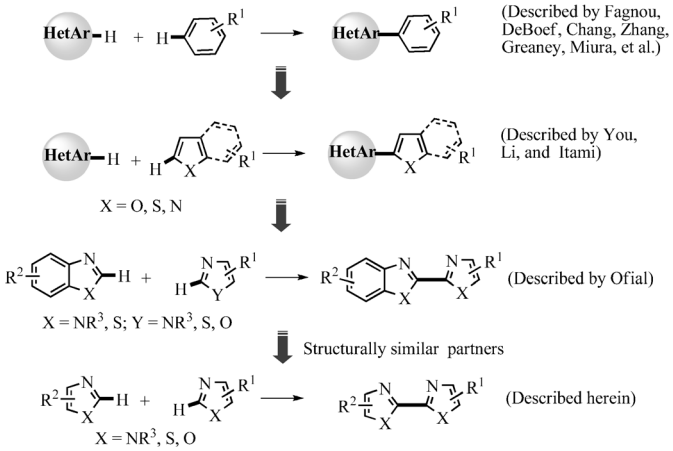
The heteroaryl–heteroaryl bond is a vital structural feature of molecules of medicinal interest, advanced materials, and naturally occurring products.[1] From the point of view of synthetic simplicity and atom economy, direct oxidative cross-coupling between two heteroarenes through a twofold C–H activation would be the most ideal route to the bi-heteroaryl linkage, which obviates the complications associated with prefunctionalization of both substrates in conventional Ar–X/Ar–M coupling reactions. However, this type of oxidative cross-coupling is particularly challenging because the reactivity/selectivity in the two metalation steps of the catalytic cycle must be well-controlled to restrain unwanted homocoupling.[2] Over the past years, a few groups published their pioneering reports on the oxidative cross-coupling reactions between a directing-group-bearing arene and an arene,[3] between two simple arenes,[4] and between an arene and a heteroarene.[5,6] Very recently, the use of palladium catalysts allows the oxidative intermolecular C–H/C–H cross-coupling of π-electron-rich thiophenes, furans, indoles and pyrroles with various important classes of heteroarenes such as xanthines, azoles, and indolizines, pyridine *N*-oxides.[7–9] It is noteworthy that all these examples require the presence of distinctly different π-electronic characteristics between two heteroarenes, which may facilitate an inversion in reactivity and selectivity.

Azoles are π-electron-excessive five-membered N-heteroarenes with a relatively acidic (sp^2) C–H bond and have a wide range of homologous families. The azole motif is one of the most abundant and relevant heterocycles in pharmaceuticals, important biologically active products, materials sciences, and natural products. Thus, from both academic and practical standpoints, interconnecting two structurally similar azoles to form unsymmetrical bisazoles would offer rich insights into the issues embedded in the metal-catalyzed oxidative C–H/C–H cross-coupling. Quite recently, Ofial and co-workers reported an efficient palladium-catalyzed dehydrogenative cross-coupling of a benzoazole (i.e., benzothiazole and benzimidazole) with an azole at the C2 and C2′ positions in the presence of $Pd(OAc)_2$ (5–10 mol%) and $Cu(OAc)_2$ (2 equiv) in combination with AgF (2 equiv) or $AgNO_3$/KF (1.5+3 equiv) at 120 °C for 24–48 h.[10] However, the two heteroarenes show a clear difference in the properties of π-conjugated systems. Naturally, we wondered whether two non-benzofused azoles with more closely related structures could selectively undergo the oxidative cross-coupling (Scheme 1).[11] However, we may face a series of obstacles: 1) Benzoazoles are more π-electron-excessive and exhibit stronger acidity at the C2 hydrogen atom than the corresponding azoles;[12] 2) C2-unsubstituted azoles are particularly prone to undergo oxidative homocoupling[13] and decomposition under the transition-metal-catalyzed oxidative conditions; and 3) unlike benzoazoles, azoles may deliver more regioisomeric products (i.e., C4/C5 besides C2).



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

In the current work, we focused on evaluating the oxidative coupling reactions of imidazoles, thiazoles, and oxazoles that are among the most common azoles. In our initial investigation, we observed that 4,5-dimethylthiazole **2a** and 5-phenyloxazole **1a** easily undergo homocoupling. Thus, two such candidate substrates were chosen as model partners,

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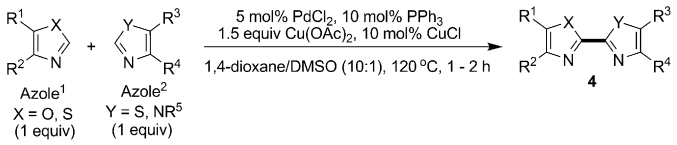
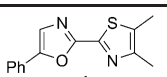
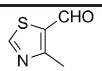
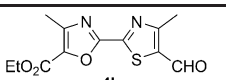
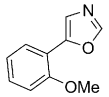
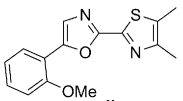
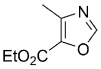
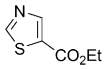
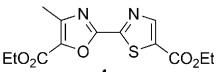
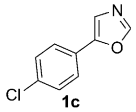
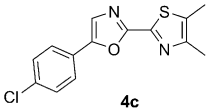
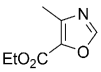
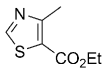
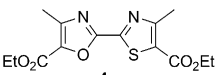
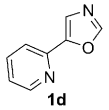
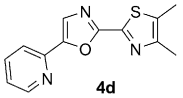
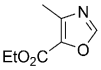
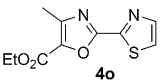
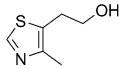
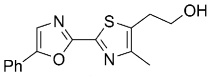
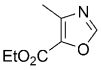
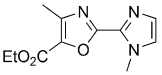
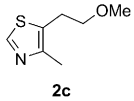
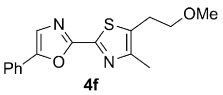
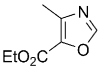
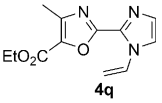
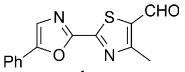
Table 1. Oxidative cross-coupling of azoles.[a,b]



	Azole[1]	Azole[2]	Heterocoupling product	Yield [%]		Azole[1]	Azole[2]	Heterocoupling product	Yield [%]
1	 1a	 2a	 4a	68, (4, 15), 86[c]	12	 1e	 2d	 4l	70, (<5, trace), 75[c]
2	 1b	 2a	 4b	70, (trace, 14), 85[c]	13	 1e	 2e	 4m	71, (<5, 15), 81[c]
3	 1c	 2a	 4c	67, (trace, 17), 74[c]	14	 1e	 2f	 4n	73, (<5, 16), 82[c]
4	 1d	 2a	 4d	66, (15, 18), 75[c]	15	 1e	 2g	 4o	58, (<5, trace), 70[c]
5	 1a	 2b	 4e	70, (11, trace), 90[c]	16	 1e	 3a	 4p	67,[c] (<5, n.d)
6	 1a	 2c	 4f	68, (9, 17), 77[c]	17	 1e	 3b	 4q	60,[c] (<5, n.d)
7	 1a	 2d	 4g	68, (11, trace), 74[c]	18	1e	3c	4r	68,[c] (<5, n.d)
8	1a	2e	4h	66, (7, 15), 72[c]	19	1e	3d	4s	66,[c] (<5, n.d)
9	1e	2a	4i	90, (trace, 5), 94[c]	20	2d	3b	4t	64,[c] (trace, n.d)
10	1e	2b	4j	73, (<5, trace), 81[c]	21	2d	3c	4u	71,[c] (trace, n.d)
11	1e	2c	4k	78, (<5, trace), 86[c]	22	2d	2h	4v	76, (trace, 14), 84[c]

[a] Reaction conditions: azole[1] (0.5 mmol), azole[2] (0.5 mmol, 1.0 equiv), $PdCl_2$ (5 mol%), PPh_3 (10 mol%), CuCl (10 mol%), $Cu(OAc)_2$ (1.5 equiv) and 1,4-dioxane/DMSO (1.0/0.1 mL) at 120°C for 1 h under N_2. [b] Isolated yields of **4**. The yields in parentheses refer to the homocoupling of azole[1] and azole[2], respectively. [c] Isolated product yields. Reaction conditions: azole[1] (0.25 mmol), azole[2] (0.375 mmol, 1.5 equiv), $PdCl_2$ (5 mol%), PPh_3 (10 mol%), CuCl (10 mol%), $Cu(OAc)_2$ (1.5 equiv) and 1,4-dioxane/DMSO (1.0/0.1 mL) at 120°C for 1–2 h under N_2 (For details, see the Supporting Information).

which gave us a great opportunity to better understand how to restrain intractable homocoupling and how to efficiently promote heterocoupling. After screening several parameters (e.g., palladium source, oxidant, ligand, additive, solvent, and time; see the Supporting Information, Table S1), the heterocoupling product **4a** was obtained in 68% yield when $PdCl_2$ (5 mol%) was used in combination with PPh_3 (10 mol%), CuCl (10 mol%), and $Cu(OAc)_2$ (1.5 equiv) in 1,4-dioxane/DMSO at 120°C for 20 h (see the Supporting Information, Table S1, entry 14). To our surprise, this transformation could be carried out even in just one hour (see the Supporting Information, Table S1, entry 17; Table 1, entry 1), whereas most of the known examples require a reaction time of one to two days.

With the optimized conditions in hand, we first inspected the scope of this protocol with respect to oxazoles and thiazoles. It was gratifying to find that a variety of oxazoles could couple with diverse thiazoles with the C2/C2′-selectivity in satisfactory yields (Table 1, entries 1–15). The C4 and/or C5 unsubstituted thiazoles were amenable to the oxidative coupling reactions at the C2 position of thiazoles in acceptable yields (Table 1, entries 8, 13, and 15). In addition to the dehydrogenative couplings between oxazoles and thiazoles, the current catalytic system was suitable for the reactions of oxazoles or thiazoles with imidazoles that are often more sluggish in reactivity than oxazoles and thiazoles (Table 1, entries 16–21). Worthy of note was that all reactions of imidazoles described herein did not give rise to unwanted bisimidazoles. The catalyst system could also smoothly accelerate the cross-coupling between two thiazoles (Table 1, entry 22). More importantly, these reaction conditions were compatible with the presence of some troublesome functional groups such as ester, aldehyde, terminal vinyl, nitro, and even free hydroxyl groups to afford highly functionalized bisazoles, which could then be subjected to further synthetic transformations. This method could be applied to azoles with the chloro substituent on the aromatic ring, which provided a complementary platform for further functionalizations through traditional transition-metal-catalyzed coupling reactions (Table 1, entry 3). The transformation was regioselective at the C2 position of azole, and other regioisomeric products were not yet observed. An X-ray analysis of single crystals **4q** confirmed that the direct C–H/C–H cross-coupling took place between the C2 and C2′ positions on the two azole rings (Figure 1).[14]

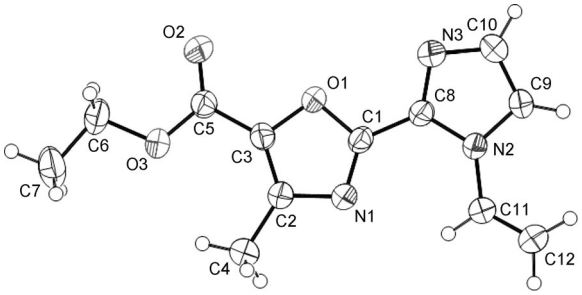
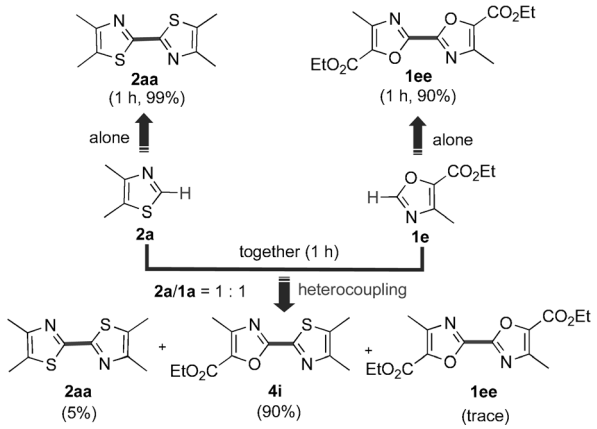


Figure 1. ORTEP diagram of **4q**. Thermal ellipsoids are shown at the 50% probability level.

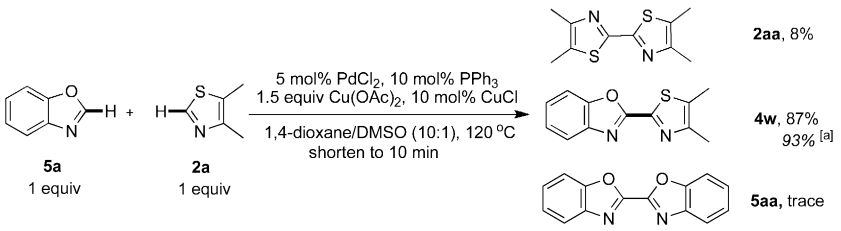
It is important to stress that the thiazoles and oxazoles investigated herein were susceptible to homocoupling to afford a symmetric bisazole under the optimized conditions (For details, see the Supporting Information, Table S2). For example, 4,5-dimethylthiazole and ethyl 4-methyloxazole-5-carboxylate alone could rapidly undergo homocoupling to give **2aa** and **1ee** in 99 and 90% yields, respectively (Scheme 2). However, when these two azoles reacted with each other in the ratio of 1: 1, the cross-coupling reaction occurred almost exclusively to deliver **4i** in 90% yield. In addition, the synthesis of **4i** was performed without problems on a gram scale, which would represent a bench-scale preparation.



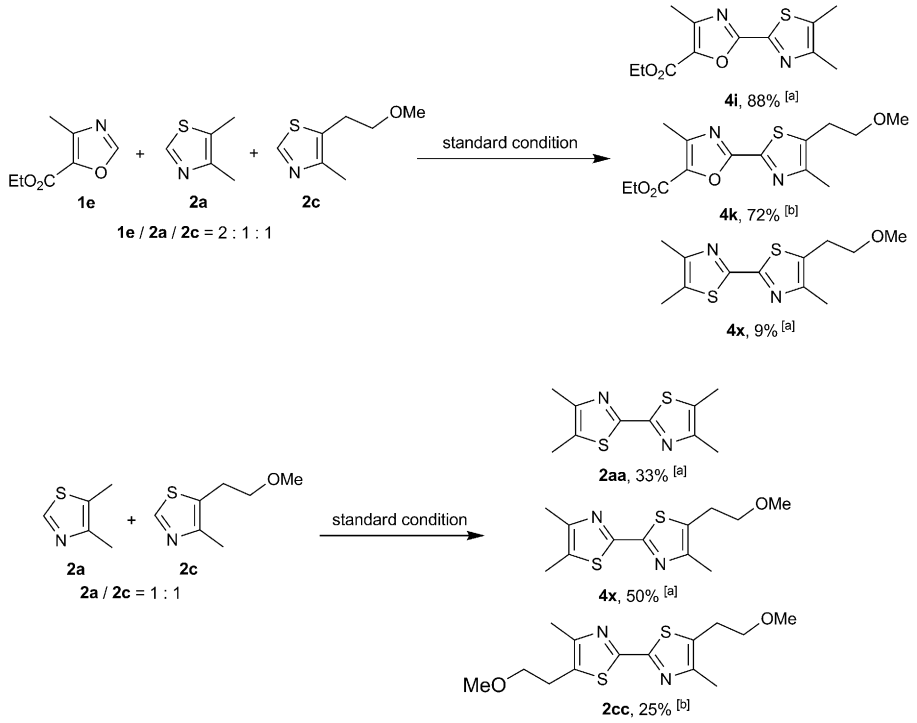
Scheme 2. Evolution of palladium-catalyzed oxidative couplings of **1e** and **2a** through double C–H activation.

The catalyst system could also be applied to the C–H/C–H cross-coupling of a series of benzofused azoles with various azoles. Considering Ofial and co-workers reported the dehydrogenative cross-couplings of benzothiazole and benzimidazoles with azoles,[10] herein we only give one example of benzoxazole shown in Scheme 3; the detailed results of these couplings will be published in due course. It is noteworthy that 93% yield of **4w** was obtained even when the reaction time was reduced to 10 min.

The previously reported examples of the oxidative cross-couplings of (hetero)arenes with arenes have often used up to 40–100 equivalents of one of the coupling components.[7b] In this work, the reactions could give satisfactory chemoselectivity even when the ratio of two partners is decreased to 1:1. To further demonstrate the overall chemoselectivity, two competition experiments were performed (Scheme 4). Oxazole **1e** and thiazoles **2a** and **2c** were added in one pot in a ratio of 2:1:1 under the standard reaction conditions; both the yields of **4i** and **4k** were much better than that of **4x**. It demonstrated that if Pd reacted with the oxazole first, then the resulting oxazole–Pd complex reacted unselectively



Scheme 3. Direct C2/C2′ cross-coupling of benzoxazole and 4,5-dimethythiazole. [a] 4,5-Dimethylthiazole (1.5 equiv) was used.



Scheme 4. Competition reactions of oxidative couplings among azoles. [a] Isolated product yields based on **2a**. [b] Isolated product yields based on **2c** (For details, see the Supporting Information).

with **2a** and **2c** (or their copper complexes). Alternatively, if Pd reacted with either of the thiazoles first, the resulting thiazole–Pd complex reacted selectively with the oxazole (or its copper complex) over another electronically similar thiazole. As compared with the coupling between thiazole **2d** with an electron-withdrawing formyl substituent and the thiazole **2h** with two inductively electron-donating alkyl groups (Table 1, entry 22), the thiazole **2a** reacted with the electronically quite similar thiazole **2c** with a ratio of 1:1 to give rise to an approximate statistical distribution of products, showing a fairly poor chemoselectivity (Scheme 4). The above observations implied that a difference in electronic characteristics between two partners might facilitate a better selectivity of heterocoupling.

To get some mechanistic insights, the following experiments were carried out. Addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 20 mol%) as a radical scavenger had a negligible effect on the reaction between **1a** and **2a**, which ruled out a radical pathway (see the Supporting Information, Table S1, entry 18). When $Cu(OAc)_2$ was replaced by $CuCl_2$ and $CuBr_2$, only a trace amount of heterocoupling product was obtained (see the Supporting Information, Table S1, entries 10 and 11). When Ag_2CO_3 was used as the oxidant, replacement of $PdCl_2$ with $Pd(OAc)_2$ improved the conversion rate of **1a** from trace to 22% (see the Supporting Information, Table S1, entries 7 and 21). These observations hinted that the acetate anion played a critical role in the transformation.

It is well known that Cu^I salts have been used as catalyst or activator in direct C–H functionalization of N-heteroarenes. Considering that the Cu^I species might be formed from Cu^{II} salts in the transformation,[15] $Cu(OAc)_2$ was replaced by Ag_2CO_3 as the oxidant to exclude the interference of Cu^{II} sources. The control experiments demonstrated that the absence of CuCl would greatly lower a conversion rate of **1a** from 85 to 22%, which clearly clarified the pivotal role of Cu^I salts (see the Supporting Information, Table S1, entries 21 and 22).

Although the mechanism is not well understood at this stage, on the basis of the above observations, we proposed that a plausible catalytic cycle could consist of 1) C–H metalation of azole to form the arylpalladium species (Azole[1])–PdL_n through a carboxylate-assisted concerted metalation-deprotonation (CMD) process, 2) reversible C–H cupration of the other azole,[5g] and subsequent transmetalation with the (Azole[1])–PdL_n species to form the key heterocoupling intermediate (Azole[1])–Pd–(Azole[2]) complex, and 3) productive reductive elimination. In addition, triphenylphosphine was supposed to stabilize the arylmetal intermediate, accelerating the transformation (see the Supporting Information, Table S1, entries 23–27).

In conclusion, we have discovered a palladium/copper cocatalytic twofold C–H activation that allows, for the first time, the chemo- and regioselective oxidative cross-coupling between two non-benzofused azoles at the C2 and C2′ positions. The catalytic system has the following features, including: 1) rapidity; 2) wide functional group tolerance; 3) high selectivity; and 4) an easily available and inexpensive catalytic system. The findings have provided us an inspiration that the difference in electronic characteristics between the two structurally similar heteroarenes would facilitate oxidative C–H/C–H cross-coupling.

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