C–H Functionalization

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Palladium-Catalyzed Dehydrogenative Cross-Couplings of Benzazoles with Azoles**

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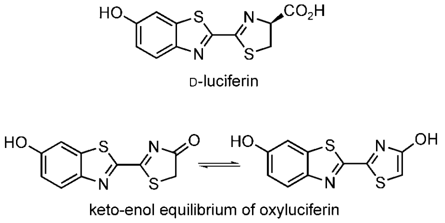
Biaryl compounds play an important role in nature and many functional materials.[1] Classical transition-metal-catalyzed methods for the synthesis of biaryls, such as Kumada, Negishi, Stille, Suzuki, and Hiyama–Denmark reactions, require functionalized arenes for the selective linkage of two arenes through a C–C bond.[2] Recently, catalytic direct arylations have emerged which avoid the introduction of functional groups in at least one of the two coupling partners prior to cross-coupling by C–H bond activation.[3] The development of direct selective intermolecular heteroarylations of heteroarenes appears particularly beneficial because prefunctionalizations of heteroarenes are often difficult. From the viewpoint of atom economy, twofold C–H bond activation is the ideal strategy for interconnecting two heteroarenes, and the groups of Fagnou and DeBoef showed independently that palladium(II) catalysis can be used for oxidative C–H/C–H cross-couplings of heteroarenes with carbocyclic arenes.[4] The $Pd(OAc)_2$-catalyzed oxidative cross-coupling of electron-deficient polyfluoroarenes with thiophenes, furans, and imidazoles was achieved by Zhang and co-workers by using Ag_2CO_3 in the presence of 1 equivalent of acetic acid.[5] Hu, You, and co-workers reported on $Pd(OAc)_2$-catalyzed copper-salt-activated C–H/C–H cross-couplings of xanthines, azoles, and electron-poor pyridine N-oxides with thiophenes and furans.[6] However, to date, efficient C–H/C–H cross-couplings between very similar partners, such as different azoles, remains a challenge because of their tendency to undergo homocoupling.[7] Hence, decarboxylative C–H arylations were employed by Zhang and Greaney to link differently substituted azoles in moderate to good yield, but homocoupling was not fully suppressed and remained a limiting factor.[8]

Though numerous natural products with important biological activities contain directly linked azoles, the 2,2′-linkage of azoles is a rare motif in nature.[9] The only prominent example is D-luciferin, which is used by firefly beetles to generate oxyluciferin in an electronically excited state (Scheme 1). Upon its return to the ground state oxyluciferin emits light in the range of 530–640 nm (bioluminiscence).[10]

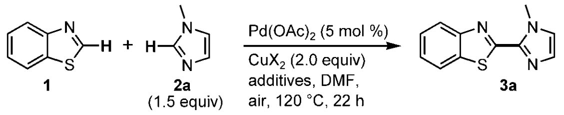


Scheme 1.

Herein we report a method for the selective C–C coupling between the nonfunctionalized C2 positions of azoles through the cleavage of two C–H bonds which provides access to a class of widely unexplored unsymmetrical 2,2′-bisheteroaryls.[11]

We chose the reaction between **1** and **2a** to optimize the conditions for the palladium-catalyzed cross-coupling reaction (Table 1). In a first series of experiments, the reactions

Table 1: $Pd(OAc)_2$-catalyzed cross-coupling of **1** with **2a**.[a]



Entry	CuX_2	Additives	Yield[b] [%]
1[c]	$Cu(OAc)_2 \cdot H_2O$	–	trace[d]
2[c]	$Cu(OAc)_2 \cdot H_2O$	AgF (2 equiv)	93
3[c]	$Cu(OAc)_2 \cdot H_2O$	KF (2 equiv)	22[d]
4[c]	–	AgF (2 equiv)	trace[e]
5	$Cu(OAc)_2 \cdot H_2O$	AgF (2 equiv)	92[f]
6	$Cu(OAc)_2 \cdot H_2O$	$KF/AgNO_3$ (3+1.5 equiv)	91 (63)[g]
7	CuF_2	AgOAc (1.5 equiv)	87
8[h]	$Cu(OAc)_2 \cdot H_2O$	$KF/AgNO_3$ (3+1.5 equiv)	31[h]
9	–	KF/AgOAc (3+1.5 equiv)	35
10	–	KF/AgOAc (3+3 equiv)	71
11	CuBr	KOAc/AgF (2+2 equiv)	84
12	$CuCl_2$	$KF/AgNO_3$ (3+1.5 equiv)	trace
13	$CuBr_2$	$KF/AgNO_3$ (3+1.5 equiv)	trace
14	$Cu(OTf)_2$	$KF/AgNO_3$ (3+1.5 equiv)	31

[a] A mixture of **1** (0.25 mmol), **2a** (0.38 mmol), $Pd(OAc)_2$ (5 mol%), CuX_2 (0.50 mmol), and additives in DMF (2.5 mL) was stirred at 120°C for 22 h under air. [b] Yield of isolated **3a** (homocoupling of either **1** or **2a** gave yields <5% if not mentioned otherwise). [c] Under oxygen atmosphere. [d] Homocoupling consumed some **2a** by formation of 1,1′-dimethyl-2,2′-biimidazole (21% yield for entry 1; 15% yield for entry 3). [e] Almost quantitative recovery of the starting materials. [f] The same yield of **3a** was obtained when TEMPO (20 mol%) was added as a radical scavenger. [g] Under an atmosphere of dry nitrogen. [h] Without $Pd(OAc)_2$; **1** was recovered with 63% yield.

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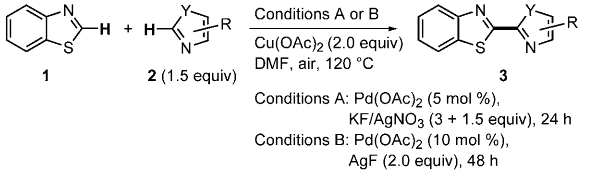
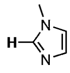
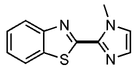
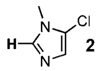
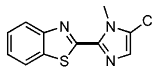
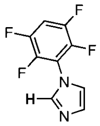
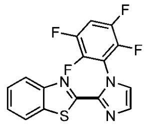
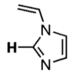
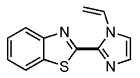
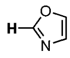
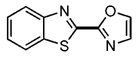
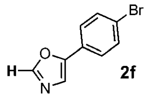
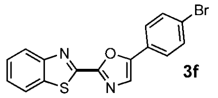
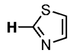
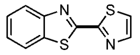
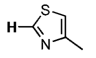
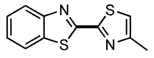
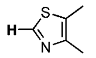
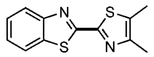
were carried out under an atmosphere of O_2 (1 atm) in *N,N*-dimethylformamide (DMF) which gives heterogeneous reaction mixtures (Table 1, entries 1–4). Whereas the presence of 2 equiv of the additive $Cu(OAc)_2{\cdot}H_2O$ was not sufficient to afford **3a**, the combination $Cu(OAc)_2{\cdot}H_2O$ (2 equiv)/AgF (2 equiv) led to the formation of **3a** in excellent yield (93 %).[12] Replacing AgF by KF diminished the yield of **3a** considerably (Table 1, entry 3). The cross-coupling failed completely when the reaction was carried out in the presence of AgF but without $Cu(OAc)_2{\cdot}H_2O$ (Table 1, entry 4). We were delighted to find that oxygen atmosphere was not necessary to achieve the cross-coupling, and **3a** was obtained in high yield when **1** and **2a** reacted under ambient air atmosphere without exclusion of moisture (92 %, Table 1, entry 5). The reliability of this coupling method was confirmed by the successful generation of **3a** on a 1 mmol scale (see the Experimental Section). The combinations $Cu(OAc)_2{\cdot}H_2O$/KF/$AgNO_3$ and CuF_2/AgOAc were as efficient as $Cu(OAc)_2{\cdot}H_2O$/AgF in mediating the formation of **3a** (Table 1, entries 5–7). These results show that the sources of Cu^{2+}, Ag^+, and AcO^- ions are not crucial for the success of the cross-coupling. Different polar aprotic solvents (e.g., DMSO, NMP) could be employed to achieve high yields of **3a**, whereas the use of protic and apolar solvents was less effective.[13]

The reaction of **1** with **2a** was significantly attenuated in the absence of the $Pd(OAc)_2$ catalyst (Table 1, entry 8). Whereas the low degree of conversion in the absence of Cu^{2+} could be partially compensated by using 3 equivalents of Ag^+ or providing CuBr (Table 1, entries 9–11),[6,14] combining Cu^{2+} and Ag^+ salts is more economical and gives superior results (Table 1, entries 5–7).

To gain further insight into the fate of the Cu^{2+} and Ag^+ ions during the cross-coupling reaction, the precipitates isolated by filtration at the end of the reactions in entries 5 and 6 of Table 1 were analyzed by X-ray powder diffraction. The diffraction patterns of the two samples were almost identical and showed significant peaks which were assigned to Ag^0 (see the Supporting Information). Hence, Ag^+ ions can be considered as terminal oxidants in these reactions.[15] The role of the Cu^{2+} ions is less clear at present. We assume that, in analogy to the Wacker process,[16] Cu^{2+} ions catalyze the oxidation of Pd^0 by O_2 when substoichiometric amounts of Ag^+ ions are applied (Table 1, entries 6 and 7). Moreover, it has been reported that $Pd(OAc)_2$ and $Cu(OAc)_2{\cdot}H_2O$ can form polymetallic acetate-bridged clusters in acetic acid.[17,18] It seems possible, therefore, that catalytically active Cu–Pd species are generated in situ also under our reaction conditions.[4b,d,19] To test this hypothesis, we varied the counterion X in the copper salt CuX_2 in the presence of KF/$AgNO_3$ and catalytic amounts of $Pd(OAc)_2$. The poor results obtained with $CuCl_2$, $CuBr_2$, and $Cu(OTf)_2$ (Table 1, entries 12–14) confirmed the crucial role of acetate ions for achieving high yields of **3a**.

Table 2: $Pd(OAc)_2$-catalyzed C2 arylation of **1** with azoles **2**.[a]



Entry	Azole **2**		Conditions	Product **3**		Yield[b] [%]
1		**2a**	A		**3a**	91
2		**2b**	B		**3b**	95
3		**2c**	B		**3c**	91
4		**2d**	A		**3d**	87
5		**2e**	B		**3e**	86
6		**2f**	B		**3f**	71
7		**2g**	A		**3g**	65
8		**2h**	A		**3h**	67
9		**2i**	A		**3i**	92

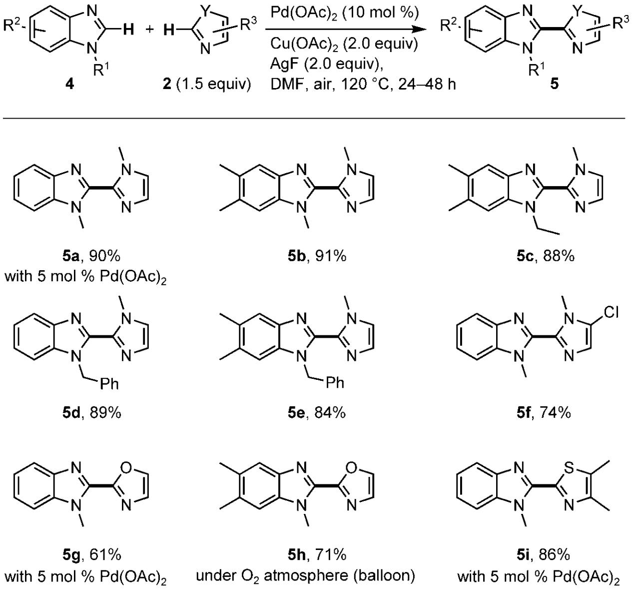
[a] A mixture of **1** (0.25 mmol), **2** (0.38 mmol, 1.5 equiv), $Pd(OAc)_2$ (5 or 10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.50 mmol), and additives (KF/$AgNO_3$ or AgF) in DMF (2.5 mL) was stirred at 120 °C for the given time under air. [b] Yield of isolated product after column chromatography.

We explored various azoles as coupling partners for **1** by employing the two equally efficient additive combinations, that is, $Cu(OAc)_2{\cdot}H_2O$ with either KF/$AgNO_3$ or AgF, in the presence of 5 to 10 mol % $Pd(OAc)_2$ as catalyst (Table 2). The cross-coupling of **1** with 5-chloro-1-methylimidazole (**2b**) furnished **3b** in excellent yield (Table 2, entry 2). Interestingly, the *N*-(2,3,5,6-tetrafluorophenyl)-substituted imidazole **2c**, which has sites for C–H activation at both rings, reacted with **1** regioselectively at C2 of the imidazole moiety to give **3c** (Table 2, entry 3). As the C–H bond at the tetrafluorinated phenyl ring in **2c** did not react in the arylation of **1**, subsequent direct functionalizations of **3c** are possible.[5,20] The reaction of **1** with **2d** delivered **3d** carrying an N-vinyl group, which could be useful for incorporating the bisheteroaryl unit into functional (co)polymers.

Further reactions of **1** with differently substituted oxazoles and thiazoles (Table 2, entries 5–9) show the versatility of this direct oxidative C–H/C–H cross-coupling methodology. Since the aryl bromide **2f** is compatible with the reaction conditions of the cross-coupling, the bisheteroaryl–

aryl scaffold of **3f** can be extended by subsequent classical palladium-catalyzed aryl couplings.

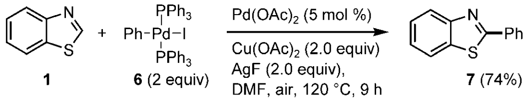
The scope of the catalytic method presented here could be extended to C2 heteroarylations of a series of benzimidazoles **4** with imidazoles, oxazoles, and thiazoles to furnish the bisheteroaryls **5a–i** (Scheme 2).



Scheme 2. Direct C2 arylation of benzimidazoles **4** with azoles **2** (yields of isolated product after column chromatography are given).

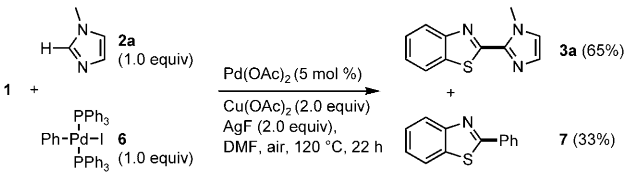
To understand the parameters that determine the selectivity for cross-coupling we compared the homocoupling reactions of **1** and **2a**. These azoles behaved differently under the reaction conditions of entry 6 in Table 1. After 9 h, GC–MS analysis showed that less than 10% of **1** had been converted, while the reaction of **2a** achieved a greater than 90% conversion.

Benzothiazole (**1**) underwent direct arylation with [*trans*-PhPdI(PPh$_3$)$_2$] (**6**) to form **7** under the reaction conditions of entry 5 in Table 1, (Scheme 3).[21]



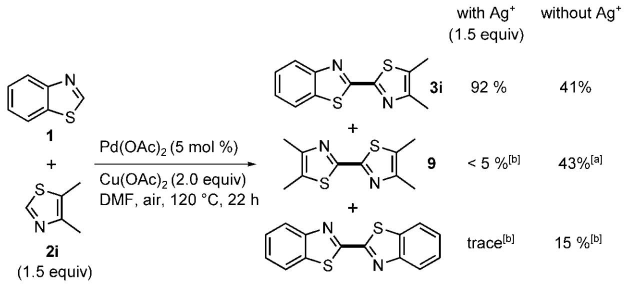
Scheme 3.

Further, a competition experiment between **1**, **2a**, and **6** gave only two main products (Scheme 4). Whereas only trace amounts of the products from homocoupling of **1**, homocoupling of **2a**, and phenylation of **2a** by **6** were detectable by GC–MS in the crude material, the yields of isolated **3a** (65%) and **7** (33%) indicate that the rate of the catalytic heteroarylation of **1** with **2a** is on the same order of magnitude as that of the direct phenylation of **1** with the aryl palladium(II) complex **6**.



Scheme 4. Competition between **2a** and **6** for benzothiazole (**1**).

We investigated the effect of the Ag$^+$ salt on the ratio of cross- and homocoupling products by studying the reaction of benzothiazole (**1**) with 4,5-dimethylthiazole (**2i**). Scheme 5 shows that the formation of homocoupling products was suppressed by the presence of Ag$^+$ ions and that cross-coupling (to **3i**) is favored under these conditions. This pivotal effect of silver(I) is presently not well understood and requires further investigation.



Scheme 5. Products of the reaction of benzothiazole (**1**) with 4,5-dimethylthiazole (**2i**) in the presence (Table 2, entry 9) and the absence of Ag$^+$ ions. [a] Yield of isolated product based on **2i**. [b] Estimated based on GC—MS analysis.

Palladium-catalyzed cross-couplings under oxidative conditions may, in principle, proceed through a Pd^0/Pd^{II} or a Pd^{II}/Pd^{IV} cycle. As diaryliodonium salts are known to oxidize Pd^{II} to Pd^{IV} species,[3 s,22] the failure of [Ph$_2$I]$^+$[PF$_6$]$^-$ (2 equiv) to transfer a phenyl group to benzothiazole (**1**) or *N*-methylimidazole (**2a**) in the presence of Pd(OAc)$_2$ as the catalyst (5 mol%) suggests that the contribution of an arylpalladium(IV) intermediate to the reaction pathway is unlikely, though we apply oxidative conditions.

Addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 20 mol%) as a radical trap to the palladium-catalyzed reaction between **1** and **2a** did not affect the yield of **3a** (Table 1, entry 5). This finding indicates that radical species do not play a decisive role in the cross-coupling process.[22c, 23]

Despite the presently rather fragmentary information on the mechanism, we propose that the Pd^{II}/Pd^0 catalytic cycle follows a C–H bond cleavage/C–H bond cleavage/C–C coupling sequence. After the first C–H bond cleavage of the azole HetAr–H and the formation of the intermediate (HetAr)–PdL$_n$, the presence of Ag$^+$ facilitates cleavage of the second C–H bond selectively at the other azole HetAr′–H. Thereby the mixed bisheteroaryl–Pd complex (HetAr)–Pd–(HetAr′) is generated as a key intermediate. A change of the mechanism for the Pd–C bond formation may account for the change of substrate selectivity between the first and the second C–H bond cleavage. Reductive elimination from the mixed bisheteroaryl–Pd complex affords the unsymmetrical 2,2′-bisheteroaryls **3** (or **5**) and a Pd^0 species. Oxidation of Pd^0 by Ag^+ (or Cu^{2+}) and binding of acetate ligands regenerates the initial Pd^{II} species and completes the catalytic cycle. According to our observations (cf. Table 1, entries 5 and 12–14), it is likely that Pd-bound acetate plays an important role as a proton acceptor during the C–H bond cleavage.

The regioselectivity of the cross-couplings is governed by the CH acidity at C2 of the azoles. However, the corresponding pK_a values[24] do not allow one to predict possible azole combinations for these reactions. Benzothiazole (**1**, pK_a 27.3) undergoes cross-couplings with oxazole (**2e**; pK_a 27.1) as well as with the much less acidic *N*-methylimidazole (**2a**; pK_a 35.1). *N*-Methylbenzimidazole (**4**, $R^1,R^2 = Me, H$; pK_a 32.5) is five orders of magnitude less acidic than **1** but reacts with the same range of azoles as **1** ($27 < pK_a < 35$).

In summary, we have developed an efficient palladium(II)-catalyzed method for the direct C2 heteroarylation of benzazoles with N-, O-, and S-containing azoles that is mediated by Cu^{2+}, Ag^+, and acetate ions and robust enough for being carried out under normal air atmosphere. Homocoupling was successfully suppressed such that mixed bisheteroaryls were obtained through the selective cleavage of C–H bonds in both substrate molecules without the requirement of prefunctionalized azoles, designed ligands, or a huge excess of one azole over the other.

In the solid state,[12] the small twist angle of 9.39(11)° between the least-squares planes of the linked heteroaryl moieties illustrates the planarity of the π system of **3a**. As the 2,2′-bisheteroaryls **3** and **5** fluoresce in $CHCl_3$ their rigidity is retained in solution (at room temperature). The biaryls **3** and **5** may, therefore, find application as versatile ligands, building blocks in organic synthesis, pharmaceuticals, and functional materials. Further investigations will concentrate on elucidating the mechanism of the reaction and extending this catalytic method to other cross-coupling reactions.

Experimental Section

Synthesis of **3a** (1 mmol scale): Under air atmosphere, a round-bottom flask was charged with $Pd(OAc)_2$ (11.3 mg, 5 mol%), $Cu(OAc)_2 \cdot H_2O$ (404 mg, 2.00 mmol), and AgF (256 mg, 2.00 mmol). Then **1** (116 μL, 1.00 mmol) and **2a** (120 μL, 1.50 mmol) were added by using microliter syringes. After the addition of DMF (2.5 mL) the mixture was stirred for 10 min at room temperature and then heated at 120 °C for 22 h. After cooling to room temperature, the reaction mixture was poured into a saturated aqueous NaCl solution (40 mL) and extracted with EtOAc (3 × 40 mL). The organic phases were combined, and the volatile components were removed in a rotary evaporator. Purification of the crude product by column chromatography (silica gel, eluent: *n*-pentane/EtOAc/NEt_3) yielded **3a** as a colorless solid (196 mg, 91%).[12]

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