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Regiodivergent Cross-Dehydrogenative Coupling of Pyridines and Benzoxazoles: Discovery of Organic Halides as Regio-Switching Oxidants

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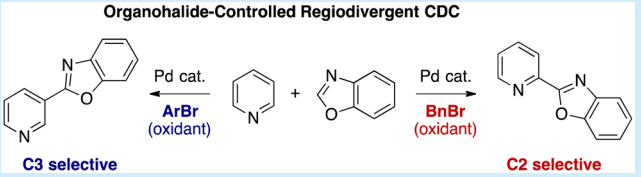
Supporting Information

ABSTRACT: Cross-dehydrogenative coupling (CDC) of two unfunctionalized heteroarenes has been recognized as an ideal transformation to synthesize privileged heterobiaryl scaffolds. However, regioselective activation and transformation of a specific set of two heterocyclic C−H bonds among other bonds have been extremely challenging. Thus, discovering a new controlling element to achieve regio-controlled and regio-divergent heterocyclic CDCs is considered crucial. In this Letter, the unprecedented use of organic halides as an oxidant to achieve the CDC reaction of pyridines and benzoxazoles with palladium catalyst is described. Moreover, the regioselectivity of the pyridine functionalization site can be controlled by the choice of organic halides.



The development of efficient methods to construct a bond between two heteroarenes has been a topic of high scientific significance in chemical synthesis due to the extensive utility of the resulting heterobiaryl derivatives in pharmaceuticals, agrochemicals, and optoelectronic materials. As a result of comprehensive investigations in the past two decades, the direct C−H arylation of heteroarenes with arylating reagents such as aryl halides and arylboron compounds has become a new standard for heterobiaryl synthesis with high practicality and predictability.[1,2] On the continuum of C−H functionalization logic in streamlined chemical synthesis, the cross-dehydrogenative coupling (CDC)[3] of two unfunctionalized heteroarenes is one of the most ideal methods for heterobiaryl synthesis, where prefunctionalization steps to prepare arylating reagents are unnecessary (Figure 1a). However, such heterocyclic CDC lags far behind other coupling techniques, because the regioselective activation and transformation of a specific set of two heterocyclic C−H bonds among other C−H bonds are extremely difficult to achieve. Thus, the development of a regio-controlled and regiodivergent heterocyclic CDC reaction by establishing a new controlling element is considered to be crucial to expand this field. In order to achieve the regiodivergent CDC of simple pyridine substrates, which are the most important[4] yet the most difficult class of heterocycles due to its relatively lower reactivity,[5−7] we envisioned that organohalides may act as a potential "functional" CDC oxidant. Although organohalides are rather underexplored as oxidants in coupling reactions,[8,9] their organic moieties could be tuned to enhance pyridine's reactivity and regioselectivity for CDC reactions. We herein introduce organic halides as a new class of "functional" oxidant that enables CDC between pyridines and benzoxazoles with a palladium catalyst (Figure 1b). Moreover, we found that the regioselectivity

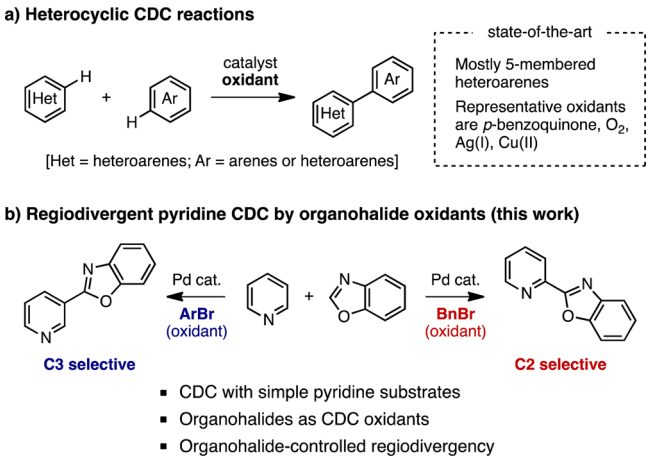


Figure 1. (a) Heterocyclic CDC reactions. (b) Regiodivergent pyridine CDC by organohalide oxidants.

of the pyridine arylation site can be switched by the choice of organohalide oxidant (C3-position with aryl bromide and C2-position with benzyl bromide).

After extensive screening of the reaction conditions along this line, we found that the use of bulky aryl bromides facilitates the palladium-catalyzed CDC reaction of pyridine and benzoxazole at the C3-position.[10,11] For example, treatment of benzoxazole (0.25 mmol) with pyridine (1.5 mL) in the presence of palladium acetate (10 mol %), 2-bromo-1,3,5-triisopropylbenzene (TIPBr:

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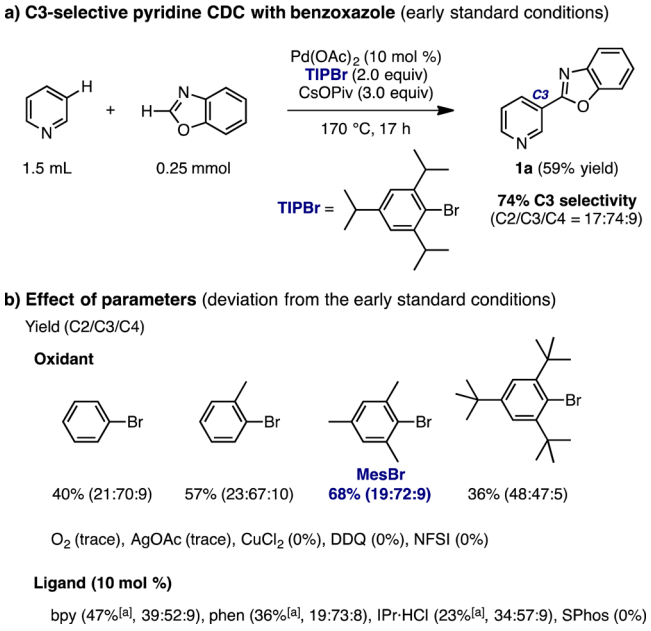

Figure 2. (a) C3-selective pyridine CDC reaction with benzoxazole. (b) Effect of parameters. [a] Determined by ^{1}H NMR analysis.

2.0 equiv), and cesium pivalate (CsOPiv: 3.0 equiv) at 170 °C for 17 h afforded the target CDC product **1a** in 59% yield (Figure 2a). The reaction took place preferentially at the C3-position of the pyridine core (C2/C3/C4 = 17:74:9). In this reaction, TIPBr functioned as an oxidant and did not act as a coupling component neither with pyridine nor with benzoxazole.[12]

Based on this discovery, we further examined the effect of parameters, such as the oxidant and the ligand in this pyridine CDC reaction system. Shown in Figure 2b are the results of screening based on the early standard conditions found in Figure 2a. As for the CDC oxidant, aryl bromides generally worked well. Interestingly, both the yield of **1a** and the C3-regioselectivity increase as the steric bulk of the aryl bromides increase. Employment of mesityl bromide (MesBr) resulted in the highest yield of 68% with a C3-selectivity of 72% (**1a**). The much bulkier 2-bromo-1,3,5-tri-(*tert*-butyl)benzene was not suitable for this reaction, as the intramolecular C−H activation preferentially proceeded to generate the corresponding benzocyclobutane as a major byproduct. Other frequently used CDC oxidants such as O_2, AgOAc, $CuCl_2$, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), and *N*-fluorodibenzenesulfonimide (NFSI) were ineffective for the present pyridine CDC reaction. It was also found that the addition of representative ligands only had detrimental effects (Figure 2b). Addition of 2,2′-bipyridine (bpy) or 1,10-phenanthlorine (phen) diminished the reaction. Employment of a *N*-heterocyclic carbene precursor (IPr·HCl: IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) or a bulky phosphine SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) suppressed the reaction, and 2,4,6-triisopropylphenylbenz[*d*]oxazole was obtained as a side product from the reaction between TIPBr and benzoxazole.

Under the established conditions [$Pd(OAc)_2$, MesBr or TIPBr, CsOPiv, 170 °C, 17 h], the CDC reaction took place with a range of pyridines and benzoxazoles (Figure 3). The best oxidant was dependent on the substrate, with TIPBr providing better results than MesBr in terms of the yield with almost the same regioselectivity except for **1b**. A variety of substituents on benzoxazole were compatible to the reaction conditions such as

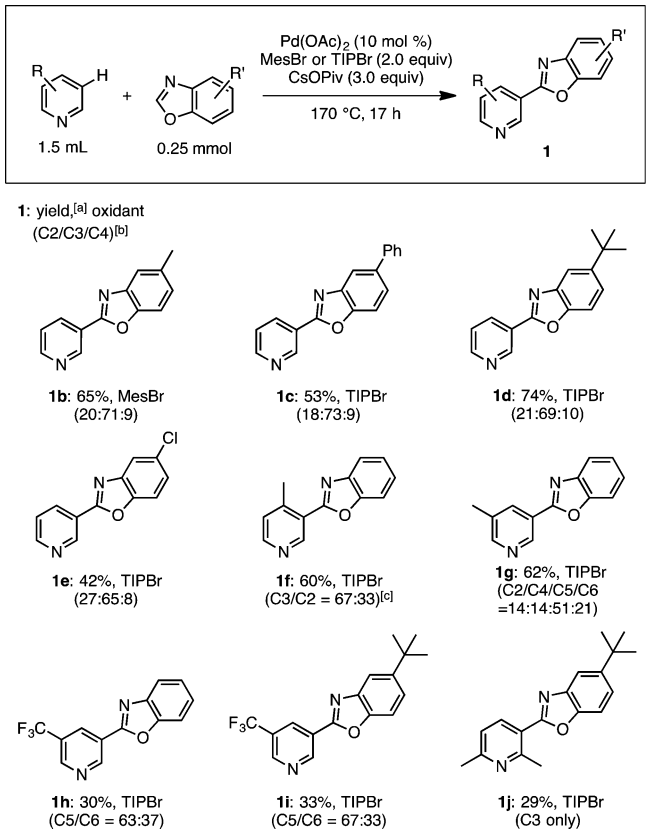

Figure 3. C3-selective CDC of pyridines with benzoxazoles. [a] Isolated yield of the mixture of regioisomers. [b] The ratio of regioisomers was determined by ^{1}H NMR analysis. [c] 5,5′-Dimethyl-2,2′-bipyridine was added as a ligand.

methyl, phenyl, or *tert*-butyl groups with good C3-selectivity. When chloro-substituted benzoxazole was employed as a coupling partner, the chloro-moiety remained intact. The reactions of substituted pyridines also showed C3-selectivity regardless of steric or electronic factors. 4-Methyl- or 3-methylpyridine afforded **1f** and **1g** in good yield with moderate selectivity. For the coupling reaction generating **1f**, the addition of 5,5′-dimethyl-2,2′-bipyridine as a ligand was important to achieve good regioselectivity. The C2/C3 ratio was almost 1:1 without the addition of the ligand. 3-Trifluoromethylpyridine underwent CDC reactions with benzoxazoles at the C5-position of the pyridine core to produce **1h** and **1i**. Sterically bulky 2,6-dimethylpyridine generated **1j** as the sole product, and no C4-arylated product was observed.[13]

During our study on the screening of oxidants, we unexpectedly discovered that benzyl bromide worked as a C2-selective oxidant (Scheme 1).[14,15] Treatment of benzoxazole (0.25 mmol) with palladium acetate (10 mol %) and CsOPiv (3.0 equiv) in pyridine (1.5 mL) at 170 °C for 17 h afforded C2-arylated pyridine **2a** in 45% yield with very high regioselectivity (C2/C3/C4 = 98:1:1).[16] Although the reason for the regioswitching was unclear at this stage, we performed several control experiments to confirm whether the labile benzyl bromide remained intact under the basic reaction conditions and worked as the oxidant (Scheme 2). Benzyl bromide may react with pyridine or cesium pivalate to form the pyridinium salt or benzyl pivalate, respectively *in situ*, which may act as a substrate or an oxidant. In order to test this possibility, we conducted the CDC reaction in the presence of benzylpyridinium bromide or benzyl

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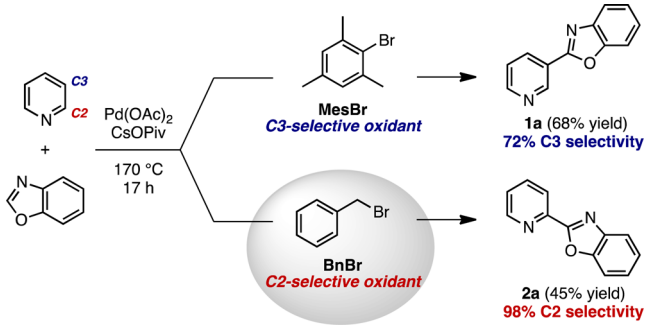
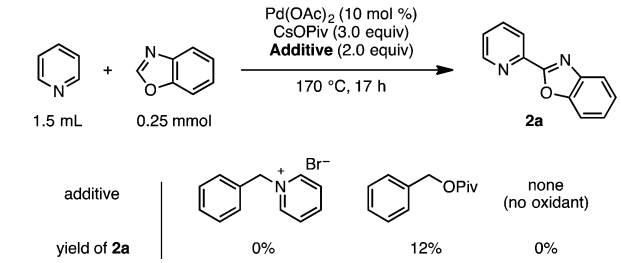
Scheme 1. Discovery of Benzyl Bromide as a C2-Selective (Regio-switching) Oxidant



Scheme 2. Addition of Possible *in Situ* Forming Oxidant



pivalate. No coupling product was observed when pyridinium bromide was used. Although benzyl pivalate worked as an oxidant, the yield was not as good as the reaction with benzyl bromide. It is noteworthy that the reaction did not proceed in the absence of an oxidant.

Pd-catalyzed heterocyclic CDC reactions have been known, but the previous examples were mainly focused on inorganic oxidants with five-membered heteroarenes.[17,18] As for the regiodivergent CDC where the regioselectivity can be switched by the reaction conditions, DeBoef[17a] and Fagnou[17b] have found that the choice of metal-based oxidants in the CDC of indoles with arenes can switch the reaction site of the indole core (C3-position with copper acetate and C2-position with silver acetate). These pioneering works and our present findings clearly show that the CDC oxidant can be a regio-controlling factor whereas the mechanism of regiodivergency is yet to be identified.[19]

Further optimization of the C2-selective reaction was then performed (see the Supporting Information for details). After a screening of ligands, IMes (1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene), an *N*-heterocyclic carbene ligand, was found to be the best ligand that afforded 54% of **2a** with exclusive formation of the C2-product (>99% C2-regioselectivity). Further screening of the catalyst precursor identified $Pd(OPiv)_2$ as the best palladium source to provide **2a** in 74% yield. The high C2-selectivity was observed for the CDC of pyridines with various benzoxazoles (Figure 4). Benzoxazoles having the phenyl, *tert*-butyl, or methoxy group were applicable to the C2-selective pyridine CDC producing **2b**−**2d** in moderate to good yields. Unfortunately, the reaction with electron-deficient benzoxazoles such as 5-trifluoromethylbenz[*d*]oxazole only led to trace amounts of the desired product. While the yields were not high, substituted pyridines were applicable to our reaction conditions and afforded C2-arylated products. The reaction of 4-trifluoromethylpyridine generated **2e** in 22% yield. When 3-methylpyridine was used as a substrate, the reactions took place at the 6-position to produce **2f** or **2g** in moderate yields. The regioselectivity was different from the Chichibabin-

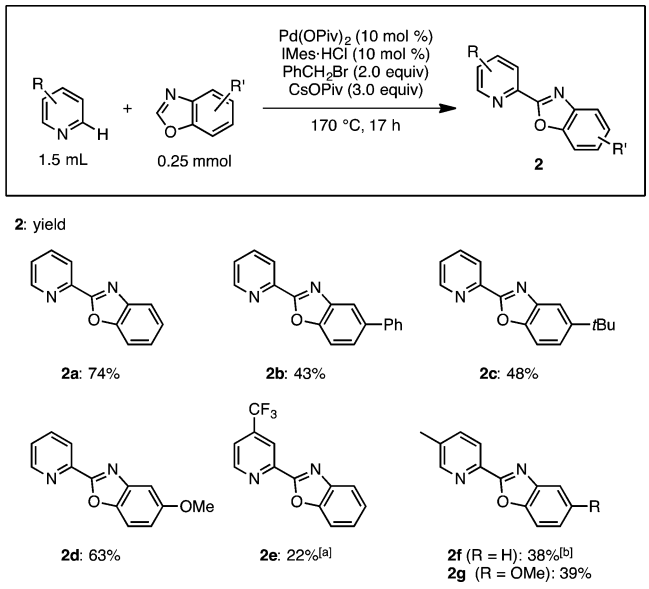


Figure 4. C2-selective CDC of pyridines with benzoxazoles. [a] The reaction with 0.75 mL of 4-trifluoromethylpyridine. [b] The reaction was performed at 150 °C.

type reaction, which occurs at the most hindered position (i.e., 2-position of 3-methylpyridine).

In summary, we have uncovered an unprecedented utility of an organic halide as an oxidant for Pd-catalyzed CDC reactions. This new class of oxidant enables the otherwise difficult CDC of pyridines and provides a new convergent synthetic strategy, as well as divergent access to various heterobiaryl structures.[20] Moreover, the regioselectivity of the pyridine functionalization site can be controlled by the choice of organic halides. The CDC reactions of pyridines with benzoxazoles took place at the C3-position of pyridine cores with aryl bromides, while the use of benzyl bromide completely switched the regiochemical outcome to the C2-selective CDC pathway. Although the detailed mechanism is still unclear at the moment, the successful regiodivergent CDC reactions bode well for the potential of organohalide control in many molecular transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00932.

Detailed experimental procedures and spectral data for all compounds, including scanned image of ^{1}H, ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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