Synthetic Methods

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Copper-Mediated C6-Selective Dehydrogenative Heteroarylation of 2-Pyridones with 1,3-Azoles**

Riko Odani, Koji Hirano, Tetsuya Satoh, and Masahiro Miura**

Abstract: *A copper-mediated C6-selective dehydrogenative heteroarylation of 2-pyridones with 1,3-azoles has been developed. The reaction proceeded smoothly by twofold C–H cleavage even in the absence of noble-metal catalysts. The observed site selectivity was directed by a pyridyl substituent on the nitrogen atom of the pyridone ring. This directing group was readily removed after the coupling event, thus leading to 2-pyridone derivatives with a free N–H group. Moreover, in some cases, catalytic turnover of the Cu salt was also possible with the ideal terminal oxidant: molecular oxygen in air.*

2-Pyridones are prevalent heterocyclic core structures in biologically active compounds and natural products.[1] Many researchers have therefore developed synthetic methods for the decoration of the pyridone ring, particularly by C–C bond formation. The most practical and reliable strategy is the palladium-catalyzed cross-coupling of halogenated pyridones with organometallic reagents.[2] On the other hand, recent advances in metal-promoted C–H activation enable the direct modification of heterocycles without prefunctionalization, for example, by halogenation and stoichiometric metalation.[3] The direct C–C coupling of 2-pyridones has also been studied (Figure 1). In 1984, Itahara and Ouseto reported a pioneering study on the palladium-mediated C5-selective direct alkenylation of 2-pyridones with acrylates.[4a] Li and co-workers subsequently developed a catalytic variant of the reaction by using $Cu(OAc)_2$ as a terminal oxidant and also succeeded in C5-selective dehydrogenative arylation with polyfluoroarenes under similar Pd/Ag catalysis.[4b] Nakao, Hiyama, and co-workers discovered a C6-selective alkenylation and alkylation with alkynes and alkenes, respectively, by elegant Ni/Al cooperative catalysts.[5] Our research group focused on the unique reactivity of carbon-centered radical species and developed a relatively challenging C3-selective direct alkylation and arylation with a Ni[6a] catalyst or a Mn[6b] salt. Very recently, a palladium-catalyzed C3-selective direct arylation with aryl boronic acids was developed by Zografos and co-workers, although the reaction is restricted to 2-pyridones that bear a hydroxy group at the C4 position.[7] Despite certain advances mentioned above, the site-selective direct functionalization of 2-pyridones still remains a challenge, in particular, unprecedented arylation at the C6 position.

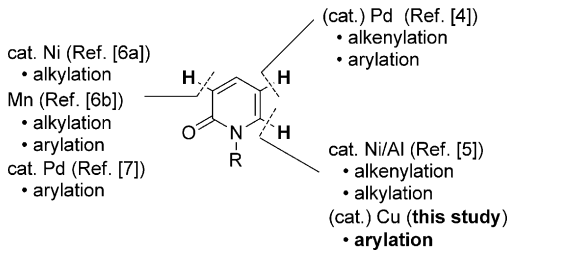
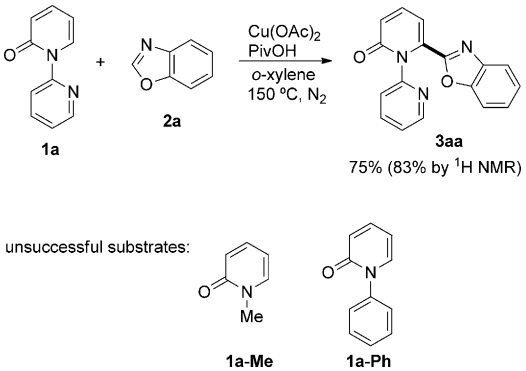


Figure 1. Reactivity profile of 2-pyridone in metal-promoted C–H functionalization.

In our continuous research on the direct and site-selective functionalization of 2-pyridones,[6] we have now developed a copper-mediated dehydrogenative heteroarylation of 2-pyridones with 1,3-azoles through twofold C–H cleavage. The reaction proceeds without any noble metals and enables, to the best of our knowledge, the first successful C6-selective direct arylation with the aid of a readily removable pyridine-based directing group. Moreover, in some cases, the process is made catalytic in Cu by the use of the ideal terminal oxidant: molecular oxygen in air.

On the basis of our recent studies on the copper-promoted C–H functionalization of (hetero)arenes,[8,9] optimization studies commenced with 1-(2-pyridyl)-2-pyridone (**1a**) and benzoxazole (**2a**). Pleasingly, we found that the C6-selective dehydrogenative arylation proceeded smoothly in the presence of $Cu(OAc)_2$ and PivOH (Piv = *tert*-butylcarbonyl) in *o*-xylene at 150 °C to give the desired product **3aa** in 75 % yield (83 % yield by NMR spectroscopy; Scheme 1). Other regioisomers were not detected at all. Control experiments



Scheme 1. Copper-mediated C6-selective dehydrogenative heteroarylation of 1-(2-pyridyl)-2-pyridone (**1a**) with benzoxazole (**2a**).

[*] R. Odani, Dr. K. Hirano, Prof. Dr. T. Satoh, Prof. Dr. M. Miura
Department of Applied Chemistry, Faculty of Engineering
Osaka University, Suita, Osaka 565-0871 (Japan)
E-mail: k_hirano@chem.eng.osaka-u.ac.jp
miura@chem.eng.osaka-u.ac.jp

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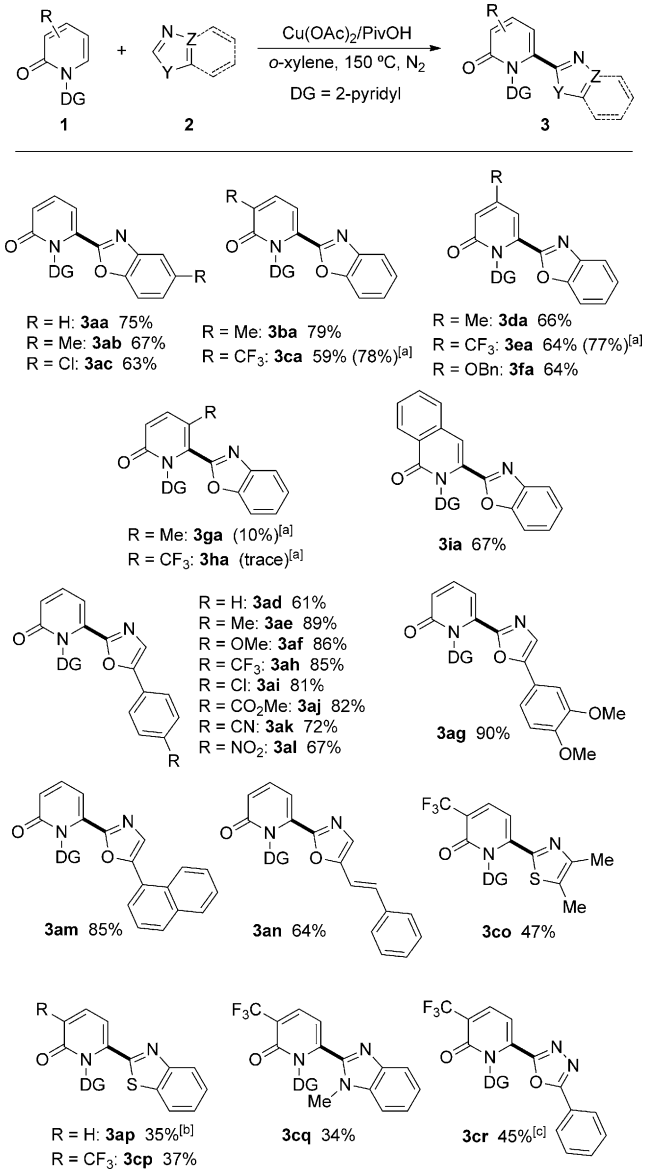
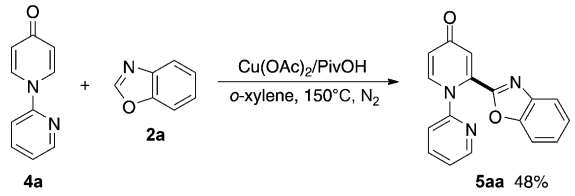
with **1a-Me** and **1a-Ph** resulted in no formation of the arylated pyridone, thus indicating the necessity of the coordinating pyridine ring in **1a**. Although the reaction occurred even without PivOH, several acidic additives improved the yield of **3aa**, and PivOH proved to be optimal.[10]

Under the conditions in Scheme 1, we evaluated the scope and limitation of the copper-mediated direct arylation of pyridones (Scheme 2). The reaction accommodated both electron-donating methyl and benzyloxy and electron-withdrawing trifluoromethyl groups on the 2-pyridone ring.



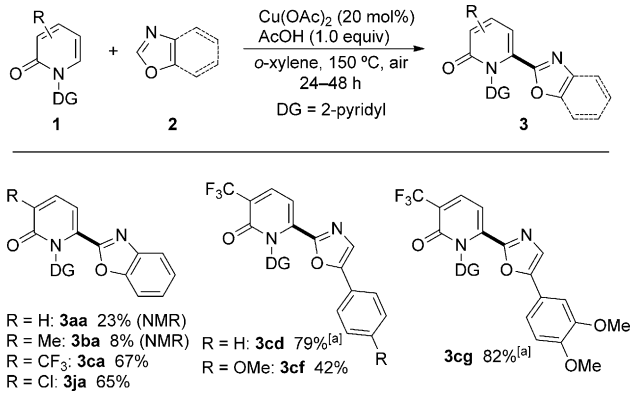
Scheme 2. Products of the copper-mediated dehydrogenative heteroarylation of various 2-pyridones with 1,3-azoles. Reaction conditions: $Cu(OAc)_2$ (0.75 mmol), PivOH (0.25 mmol), **1** (0.25 mmol), **2** (0.50 mmol), *o*-xylene (1.5 mL), 150 °C, 20 h, N_2. The yield after purification is provided. [a] The yield estimated by ^1H NMR spectroscopy is in parentheses. [b] The reaction was carried out with $Cu(OPiv)_2$ instead of $Cu(OAc)_2$ and PivOH. [c] The reaction was carried out with **2** (1.0 mmol) at 110 °C. Bn = benzyl.

Irrespective of the position of the substituent, the direct arylation occurred exclusively at the C6 position (products **3ba–fa**); however, a substituent at the C5 position was detrimental, probably as a result of steric factors (products **3ga** and **3ha**). A fused 2-isoquinolinone also coupled with **2a** to afford **3ia** in satisfactory yield. The generality of the 1,3-azole coupling partner was next examined. Benzoxazoles bearing methyl and chloro groups showed similar reactivity (products **3ab** and **3ac**). Various monocyclic 5-aryl oxazoles also underwent this transformation. The copper-based system was compatible with electronically diverse functionalities, including methyl, methoxy, trifluoromethyl, chloro, methoxycarbonyl, cyano, and nitro substituents (products **3ae–al**). Additionally, naphthyl- and styryloxazoles underwent the reaction without any difficulties (products **3am** and **3an**). Thiazole derivatives were also applicable substrates, the transformation of which provided **3co**, **3ap**, and **3cp**. Moreover, a benzimidazole and a 1,3,4-oxadiazole were transformed into **3cq** and **3cr**, albeit in moderate yield. Among other heteroarenes tested, *N*-methyl-3-cyanoindole was also reactive, although the product was formed in lower yield (ca. 20%, data not shown). On the other hand, a constitutional isomer of **1a**, that is, 4-pyridone **4a**, could be arylated selectively at the C2 position (Scheme 3), thus suggesting that the site selectivity is controlled by pyridine coordination rather than the innate electronic and steric nature of the pyridone nuclei.[11]



Scheme 3. Copper-mediated C2-selective dehydrogenative arylation of 4-pyridone **4a** with benzoxazole (**2a**).

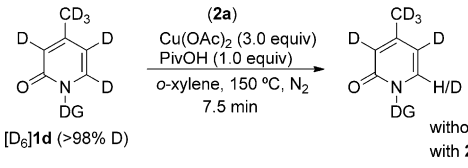
The above dehydrogenative arylation was mediated by low-toxic and inexpensive copper alone, which deserves much attention because related direct arylation reactions of heterocycles generally require noble transition metals, such as Pd, Rh, and Ru, in conjunction with a stoichiometric amount of a copper- or silver-based oxidant.[12] Furthermore, our additional investigation identified, in some cases, molecular oxygen in air to be a suitable terminal oxidant for the catalytic turnover of Cu: The 3-trifluoromethyl-2-pyridone **1c** reacted with benzoxazole (**2a**) smoothly even in the presence of 20 mol% of $Cu(OAc)_2$ and AcOH[13] (1.0 equiv) in air to furnish **3ca** in comparable yield to that observed with the standard procedure with an excess of $Cu(OAc)_2$ (Scheme 4). The catalytic conditions were also compatible with the 3-chloro-2-pyridone **1j**, which was an unsuitable substrate under stoichiometric conditions owing to competitive protodechlorination (product **3ja**). Besides benzoxazole (**2a**), 5-aryl oxazoles were promising coupling partners under Cu/O_2 catalysis (products **3cd**, **3cf**, and **3cg**). However, the parent



Scheme 4. Products of the Cu/O_2-catalyzed dehydrogenative heteroarylation of various 2-pyridones with 1,3-azoles. The yield after purification is provided. [a] The reaction was carried out with air (56 mL, 0.50 mmol based on O_2) under N_2.

pyridone **1a** and methyl-substituted **1b** showed less efficiency, and **3aa** and **3ba** were detected by NMR spectroscopy in only 23 and 8% yield, respectively. Although the exact reason for this poor reactivity is not clear at this stage, products **3aa** and **3ba** chelate tightly to the Cu center through N,N double coordination to prevent catalyst regeneration (see below), whereas the electron-withdrawing trifluoromethyl and chloro moieties in **3ca** and **3ja** facilitate dissociation of the products from Cu.[14]

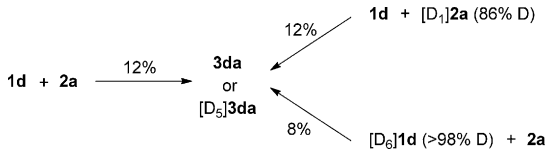
To get some mechanistic insight into the C–H cleavage step, we carried out the following deuterium-labeling experiments. At an early stage of the reaction, the deuterated pyridone [D_6]**1d** underwent H/D exchange, which was accelerated by the coupling partner, benzoxazole (**2a**) [Eq. (1)]. Combined with our previous finding that the H/D



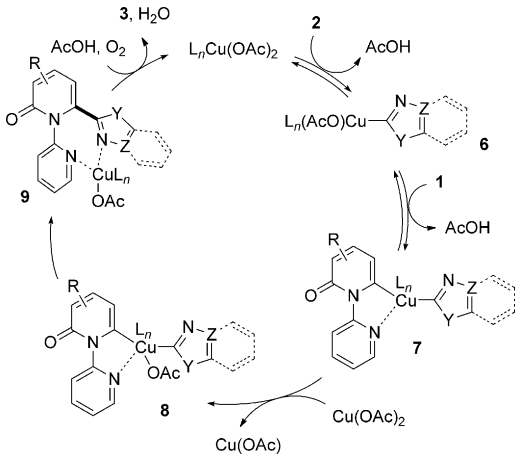
(1)

[a] The coupling product was formed in 8% yield.

scrambling of deuterated benzoxazole [D_1]**2a** occurred much faster under similar reaction conditions,[8a–d,g] this result suggests that the C–H cleavage process of both the pyridone and the azole is facile and reversible in the present copper-based system. Additionally, minor differences in product yields were observed with [D_6]**1d** and [D_1]**2a** in the initial stage of the reaction (Scheme 5), thus suggesting no rate-limiting C–H cleavage. On the basis of the above results and previously reported studies, we are tempted to assume a reaction mechanism as shown in Scheme 6. Thus, sequential C–H cupration of the 1,3-azole and the pyridone generates an organocopper intermediate **7**. The former step is promoted by the relatively high acidity of the 1,3-azole C–H atom,[15] and the latter by chelation of the pyridine moiety to the Cu center. Although the indicated metalation order (1,3-azole then



Scheme 5. Comparison of the yields of **3da** or [D_5]**3da** formed in the initial stage of reactions with deuterium-labeled **1d** or **2a**. Reaction conditions: $Cu(OAc)_2$ (0.75 mmol), PivOH (0.25 mmol), **1d** or [D_6]**1d** (0.25 mmol), **2a** or [D_1]**2a** (0.50 mmol), *o*-xylene (1.5 mL), 150 °C, N_2, 7.5 min.

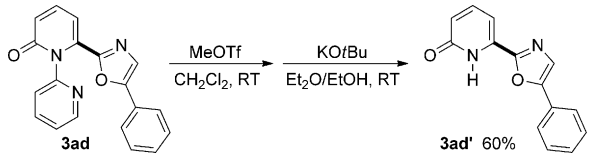


Scheme 6. Plausible mechanism. L = AcOH, O_2, or solvent.

pyridone) is supported by rates of H/D exchange of each substrate, an alternative order cannot be excluded at this stage. Subsequent oxidation-induced (disproportionation-induced) reductive elimination via the Cu^{III} species **8**[16] forms the product-ligated Cu^{I} complex **9**. Final product dissociation and reoxidation of the liberated Cu^{I} with molecular oxygen regenerate the starting Cu^{II} species to complete the catalytic cycle. When electron-neutral or electron-rich pyridones are employed (i.e., R = H or Me), the dissociation process is disfavored, thus retarding the catalyst turnover. Given the reversibility in the C–H cupration of both substrates, the product-determining step might be irreversible oxidation or reductive elimination. The exact role of external acid additives remains unclear, but they can assist C–H cleavage through concerted metalation–deprotonation.[17] Further efforts are essential for clarification of the detailed mechanism.[18]

Finally, we investigated the removal of the 2-pyridyl directing group from the product. To our delight, the deprotection occurred readily at room temperature by quaternarization-driven[19] alcoholysis to furnish the corresponding heteroarylated 2-pyridone **3ad′** with a free N–H group in acceptable yield (Scheme 7).

In conclusion, we have developed a pyridine-directed, copper-mediated dehydrogenative C6-heteroarylation of 2-pyridones with 1,3-azoles. To the best of our knowledge, this reaction is the first successful highly site selective direct arylation of a 2-pyridone ring at the C6 position. Furthermore, the directing group can be removed readily after the



Scheme 7. Removal of the 2-pyridyl directing group. Tf = trifluoromethanesulfonyl.

coupling event. In some cases, molecular oxygen in air makes the reaction catalytic in copper; the reported method is then an ideal and environmentally benign C–C bond-forming process with H_2O as the sole by-product. In ongoing studies, we seek to increase the turnover number of the Cu catalyst and expand the scope of the reaction under catalytic conditions as well as to develop related C–H activation processes under Cu catalysis.

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Keywords: arylation · C–H cleavage · copper · pyridones · synthetic methods

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[13] We have no explanation why AcOH was more effective than PivOH under catalytic conditions, but excess PivOH (with respect to Cu) shut down the reaction. A similar trend was observed in a previous study (see Ref. [8b]).

[14] Indeed, the addition of a catalytic amount of **3aa** interfered with the reaction of **1c** and **2a** under catalytic conditions. Additionally, the reaction rate of **1a** with **2a** decreased as the amount of product **3aa** increased, even under stoichiometric conditions. In contrast, no such trend was observed in the formation of **3ca**. See the Supporting Information for details.

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