Oxidative Cross-Coupling

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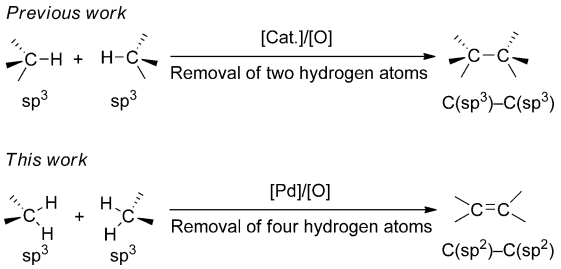
# Palladium(II)-Catalyzed Dehydrogenative Cross-Coupling between Two $C_{sp^3}$–H Bonds: Unexpected C=C Bond Formation**

*Gaocan Li, Shengyou Qian, Chunxia Wang, and Jingsong You**

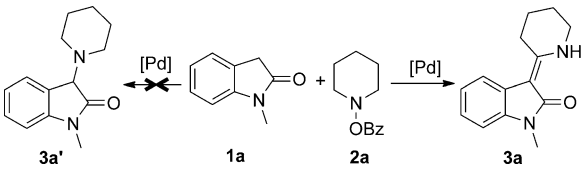
Developing efficient synthetic methods for the formation of carbon–carbon bonds is crucial for organic synthesis. In recent years, transition-metal-catalyzed $C_{sp^3}$–H functionalization to forge $C_{sp^3}$–$C_{sp^1}$, $C_{sp^3}$–$C_{sp^2}$, and $C_{sp^3}$–$C_{sp^3}$ bonds has attracted much attention.[1] From the step-economic and academic perspective, the dehydrogenative cross-coupling of $sp^3$-hybridized C–H bonds with other C–H bonds is one of the most attractive, yet most challenging, methods of carbon–carbon bond construction without the need for time-consuming prefunctionalization of both substrates. Lately, the dehydrogenative cross-coupling of α-$C_{sp^3}$–H bonds of amines, ethers, allylic and benzylic groups, and alkane $C_{sp^3}$–H bonds with a wide range of $C_{sp^3}$–H bonds has evolved into a powerful strategy for forming new $C_{sp^3}$–$C_{sp^3}$ bonds (Scheme 1 a). These




***Scheme 1.*** Transition-metal-catalyzed dehydrogenative cross-coupling between two $C_{sp^3}$–H bonds.

oxidative cross-coupling reactions usually involve ionic or radical intermediates (single electron transfer (SET) process) in the presence of transition-metal catalysts (mainly copper and iron salts) and oxidants such as *tert*-butyl hydroperoxide, hydrogen peroxide, dioxygen, benzoquinone (BQ), and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[1d–f,2] Despite the great advantage of this method, to date no studies have addressed the formation of C=C bonds, $C_{sp^2}$–$C_{sp^2}$, through a dehydrogenative cross-coupling between two $C_{sp^3}$–H bonds with the loss of four hydrogen atoms (Scheme 1 b).

Oxindoles (indolin-2-ones)[3–5] and benzofuran-2-ones[6] are prevalent in many natural products and pharmaceutical targets, and are also versatile building blocks for the synthesis of structurally complex and biologically active compounds. In particular, the 3-methyleneindolin-2-one derivative is an important subclass found in numerous pharmacologically important natural and synthetic compounds.[7] 3-(Aminomethylene)-2-oxoindolines exhibit GABAeric neurotransmitter inhibitor properties (Pfizer).[7a] In recent years, the development of methods for the C3-functionalization of indolin-2-ones has been an active area of intensive research.[3,8] On the other hand, six-membered-ring nitrogen-containing heterocyclic alkaloids are also widely present in natural products and important biologically active molecules. In an effort to explore the palladium(II)-catalyzed direct amination of the C3–H bond of indolin-2-ones[5f,g] with cyclic *O*-benzoyl hydroxylamines, which have been widely used as aminating reagents,[9] an unexpected dehydrogenative cross-coupling reaction between two $C_{sp^3}$–H bonds occurred to afford 3-(aminomethylene)-2-oxoindoline **3a** instead of 3-amino-2-oxoindoline **3a′** [Eq. (1); Bz = benzoyl]; a result




(1)

that was confirmed by single crystal X-ray diffraction (Supporting Information, Figure S2).[10] To the best of our knowledge, this is the first example of C=C bond formation through a palladium(II)-catalyzed oxidative $C_{sp^3}$–H/$C_{sp^3}$–H cross-coupling reaction.

After the surprise observation that 1-methylindolin-2-one **1a** and piperidin-1-yl benzoate **2a** underwent oxidative $C_{sp^3}$–H/$C_{sp^3}$–H cross-coupling to give the olefin 3-(aminomethylene)-2-oxoindoline (**3a**) in the presence of $Pd(OAc)_2$, we set out to optimize the reaction conditions. Several parameters (including, metal catalyst, base, solvent, and temperature) were investigated, as shown in Table S1. The catalytic system comprised of $[Pd(cod)Cl_2]$ (5 mol%; cod = 1,5-cyclooctadiene) as the catalyst, and $K_3PO_4$ (3.0 equiv) as the base in 1,4-dioxane at 110°C for 18 h afforded a 94% yield of **3a** (Table S1, entry 16). Notably, iron and copper salts, which have been extensively used as catalysts in the dehydrogenative cross-coupling between two $C_{sp^3}$–H bonds, did not promote any coupling reactions between **1a** and **2a** (Table S1, entries 17–20).

[*] G. Li, S. Qian, C. Wang, Prof. Dr. J. You
Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Medical School, Sichuan University
29 Wangjiang Road, Chengdu 610064 (PR China)
E-mail: jsyou@scu.edu.cn

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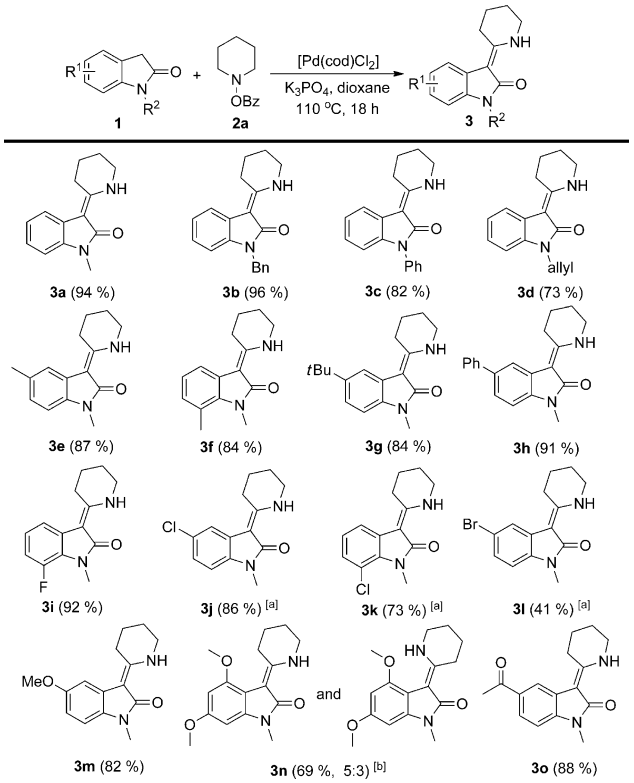
The transition-metal-catalyzed oxidative $C_{sp^3}$–H/$C_{sp^3}$–H cross-coupling reactions of indolin-2-ones have been surprisingly underdeveloped thus far, although the C3-functionalized indolin-2-ones are ubiquitous units in many natural products, biologically active molecules, and pharmaceuticals. We rationalized that the bottleneck in these types of oxidative reactions could be attributed to the C3-position of indolin-2-ones being particularly susceptible to oxidation. Thus, the discovery of an efficient and mild oxidant would be a key to overcoming this substantial hurdle. In the current catalytic system, *O*-benzoyl hydroxylamine itself serves as both the oxidant and the coupling substrate, and piperidine, as the reductive product of piperidin-1-yl benzoate, was clearly observed by GC-MS (for details, see the Supporting Information).[11] In fact, the addition of 2,2,6,6-tetramethylpiperidin-1-yl benzoate (TEMPOBz) resulted in improved yield (Table S1, entry 12 vs. entry 13), whereas the addition of extra oxidants such as copper or silver salts greatly decreased the yield of the heterocoupling products. Furthermore, the reaction of 1-methylindolin-2-one (**1a**) with piperidine, 1-methylpiperidine, or 1-benzylpiperidine instead of piperidin-1-yl benzoate (**2a**) did not occur, even in the presence of extra oxidant, which implies the key role of the *N*-benzoate group.

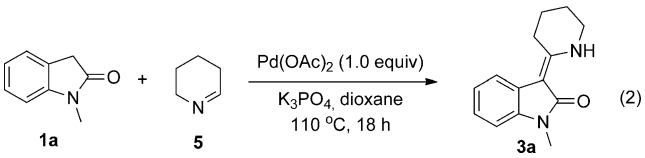
With the optimized conditions in hand, the range of indolin-2-ones was tested, as summarized in Scheme 2. We were delighted to find that a broad range of N-substituted indolin-2-ones gave the desired products in good to excellent yields. The catalytic system was compatible with a variety of functional groups on both the aromatic moiety and the N1-substitutent of indolin-2-ones. Although indolin-2-ones are known to go through palladium-catalyzed direct C–H arylation with aryl halides in the presence of base,[8a,b] it is important to stress that the halogen atoms (F, Cl, Br), which may be subjected to further synthetic transformations, were well tolerated in the current catalytic system (**3i**–**3l**, Scheme 2). Moreover, the reaction of 5-acetyl-indole-2-one also proceeded well (**3o**, Scheme 2).

To further expand the scope of the method, the cross-coupling of various *O*-benzoyl hydroxylamines was investigated (Scheme 3). It was gratifying to observe that a variety of piperidin-1-yl benzoates worked well in our catalytic system (**4a**–**4d**, Scheme 3). Morpholino benzoate was also capable of undergoing the coupling reaction (**4e**, Scheme 3).[12] Benzofuran-2-ones also smoothly furnished the desired products with satisfactory yields (**4f**–**4j**, Scheme 3).

The oxidative coupling mechanism of α-$C_{sp^3}$–H bonds of amines by a SET process is usually proposed to involve an iminium ion intermediate, which is attacked by a nucleophile to afford the desired product (Scheme 4).[1,13] Although the reaction mechanism is not very clear at present, a radical pathway can be ruled out through investigation of the effect of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) on the coupling reaction of **1a** with **2a** (for details, see the Supporting Information). GC-MS and $^1$H NMR analysis further revealed the formation of 2,3,4,5-tetrahydropyridine (**5**) in the catalytic system (for details, see the Supporting Information).[9e,14] Subsequently, **5** was synthesized according to a literature procedure.[14a] In the presence of $Pd(OAc)_2$ (1.0 equiv), the treatment of 1-methylindolin-2-one **1a** with **5** delivered the desired product **3a** in 23% yield with the recovery of **1a** in 58% yield [Eq. (2)]. In spite of the low yield of the desired product (probably owing to the instability of 2,3,4,5-tetrahydropyridine in the current catalytic system), these observations suggest that 2,3,4,5-tetrahydropyridine might be the real coupling partner.



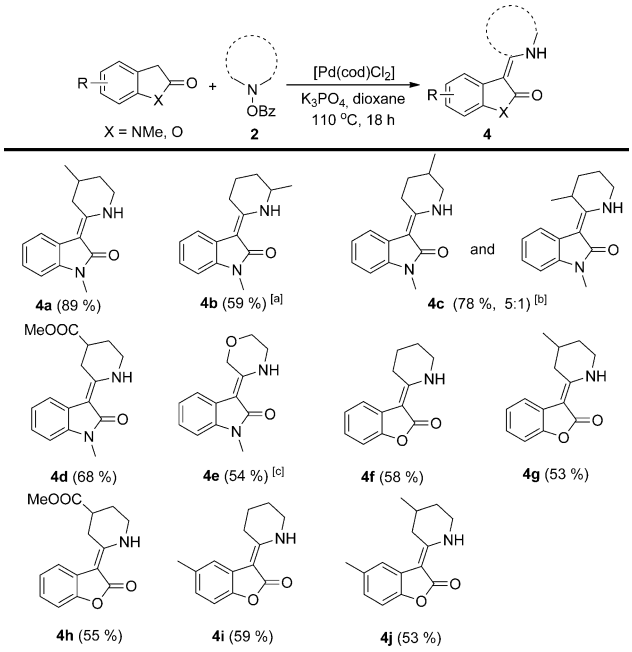

***Scheme 2.*** Cross-coupling of piperidin-1-yl benzoate **2a** with a variety of indole-2-ones **1**. Reactions were performed in the presence of indole-2-one (0.3 mmol), piperidin-1-yl benzoate **2a** (0.9 mmol), [Pd(cod)$Cl_2$] (5 mol%), and $K_3PO_4$ (3.0 equiv) in 1,4-dioxane (2.0 mL) at 110°C for 18 h. Yields of isolated products are shown in parentheses. [a] 6 h. [b] *Z*/*E* isomer ratios were determined by $^1$H NMR spectroscopy, and are shown in parentheses.



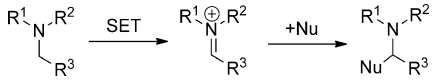

(2)

On the basis of these observations, a tentative catalytic cycle was proposed (Scheme 5). First, a palladation occurrs at the 3 position of 1-methylindolin-2-one **1a**, because of its acidic C3–H bond ($pK_a = 18.5$), to generate the intermediate **IM1** in the present of base.[1a,8a] Next, **IM1** reacts with 2,3,4,5-tetrahydropyridine (**5**), which is generated in situ from piperidin-1-yl benzoate (**2a**), to form the key palladium intermediate **IM2**. Alternatively, the formation of a palladated

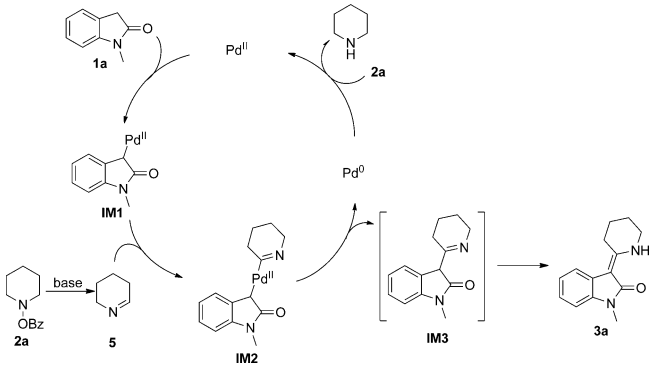
  




***Scheme 3.*** Cross-coupling of indole-2-one or bezofuran-2-ones with a variety of *O*-benzoyl hydroxylamines. Reactions were performed in the presence of indole-2-one or bezofuran-2-one (0.3 mmol), *O*-benzoyl hydroxylamine (0.9 mmol), $[Pd(cod)Cl_2]$ (5 mol%), and $K_3PO_4$ (3.0 equiv) in 1,4-dioxane (2.0 mL) at 110°C for 18 h. Yields of isolated products are shown in parentheses. [a] $Pd(cod)Cl_2$ (10 mol%). [b] Regioselectivity determined by $^1H$ NMR spectroscopy, and shown in parentheses. [c] $PPh_3$ (10 mol%).




***Scheme 4.*** Oxidative coupling of $\alpha$-$C_{sp^3}$–H bonds of amines with nucleophiles through an iminium ion intermediate. Nu = nucleophile, SET = single electron transfer.




***Scheme 5.*** Proposed catalytic cycle of the cross-coupling.

species from the reaction of **5** with $Pd^{II}$ might be another way to generate the **IM2**.[8a] Reductive elimination of **IM2** and subsequent tautomerization would then afford the desired product. The possibility of insertion of the C=N bond of **5** into the C–Pd bond of **IM1**, followed by dehydrogenation to give the desired product could not be excluded. Finally, $Pd^0$ could be reoxidized to $Pd^{II}$ to realize the catalytic cycle with piperidin-1-yl benzoate **2a**, which could also serve as a hydrogen acceptor.

In summary, we have discovered for the first time a method for constructing new C=C bonds through palladium-catalyzed oxidative cross-coupling between two $C_{sp^3}$–H bonds. The palladium(II)-catalyzed dehydrogenative cross-coupling reactions of indolin-2-ones with *O*-benzoyl hydroxylamines afford versatile 3-(aminomethylene)-2-oxoindolines in the absence of an extra oxidant. The reaction conditions are very simple, and tolerate an array of functional groups, including ester, acetyl, methoxy, fluoro, chloro, and bromo groups. Aside from acting as an aminating reagent, *O*-benzoyl hydroxylamines have herein been endowed with a novel function as the nucleophilic reagent for C=C bond formation. We anticipate that this unexpected finding may have a broader impact on the construction of other types of C=C bonds.

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[10] CCDC 933727 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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