C–H Activation

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Multiple C–H Activations To Construct Biologically Active Molecules in a Process Completely Free of Organohalogen and Organometallic Components**

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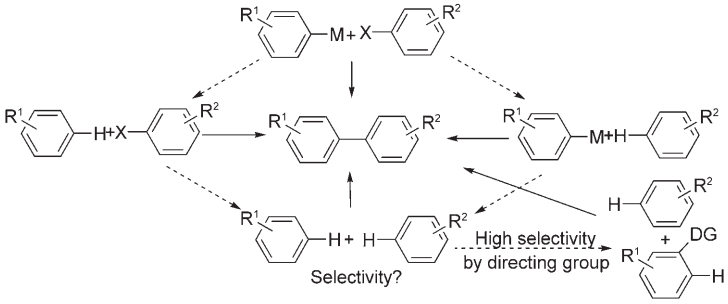
C–H functionalization is the most sustainable and straightforward method to construct complicated structures and has received significant attention in the past several decades.[1] Through direct C–H functionalization, C–C and C–X bonds (X = B, N, O, etc.) could be directly constructed by methods utilizing ruthenium, rhodium, palladium, iridium, and other metal complexes as catalysts.[2] Compared with the activation of sp^3 C–H bonds, many efforts have been made to activate sp^2 C–H bonds, especially aromatic ones, since unsaturated rings form the main scaffold in many natural products, synthetic drugs, and materials.[3] Among various methods to activate C–H bonds of aromatic rings, Pd^{II}-catalyzed electrophilic substitution is one of the most important.[4] Despite previous research, efficient methods to construct complicated scaffolds are still rare.[5] We present herein a new pathway to approach highly selective cross-coupling of arenes controlled by directing groups. This effective method is applied to prepare fully functionalized carbazoles through Pd^{II}-catalyzed multiple C–H functionalization in the absence of halides and organometallic reagents.

General methods to construct biaryls typically use transition-metal-catalyzed coupling reactions in which the arenes are functionalized with boron (or other metals) and halides.[6] Recent efforts have made this coupling more efficient by avoiding the use of one of the coupling partners through direct activation of aromatic C–H bonds.[7] Homocoupling of arenes catalyzed by palladium has been relatively well developed.[8] Cross dehydrogenative coupling (CDC)[9] of different arenes is still a big challenge for organic chemists, especially with control of chemo-, regio-, and even stereoselectivity. A recent article reported an improvement in selectivity of this cross-coupling reaction by tuning the high ratio of two different arenes, although the reaction proceeded with lower efficiency.[10] The groups of Fagnou[11] and DeBoef[12] reported the arylation of electron-rich *N*-acetylindoles and benzofurans by cross-coupling through dual C–H activation in systems in which homocoupling is inhibited. The regioselectivity of this cross-coupling was relatively well-controlled by electrophilic features of the heterocyclic scaffold; however, the process is still limited to *N*-acetylindoles and benzofurans and cannot be



Scheme 1. Construction of biaryls by different cross-coupling methods. DG = directing group

applied to other arenes to construct, for example, functionalized biphenyls. Our strategy to overcome this challenge and to gain high regioselectivity is to initiate cross-coupling with a directing group (Scheme 1).

We first tried the arylation of *N*-acetyl-1,2,3,4-tetrahydroquinoline (**1a**), which had shown relatively high reactivity in previous studies.[13] We found that the arylation between **1a** and *o*-xylene (**2a**) took place smoothly in the presence of $Pd(OAc)_2$ (10 mol%) as a catalyst with $Cu(OTf)_2$ (20 mol%) as an oxidative cocatalyst [Eq. (1)]. Gratifyingly, dioxygen (O_2, 1 atm) could be applied as the terminal oxidant to complete this transformation. The desired *ortho*-arylated product **3aa** could be isolated in 78% yield using 6.0 equivalents of **2a**. Only a single product was isolated, and the highly regioselective reaction proceeded at the *ortho* position of **1a** and the *meta* position of **2a**. In the proposed mechanism (Scheme 2), the selectivity in this arylation was most likely controlled by the acetamino directing group in the first C–H

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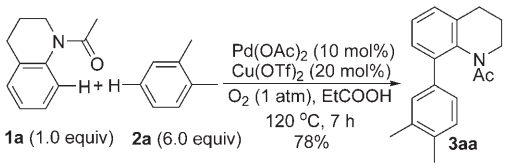
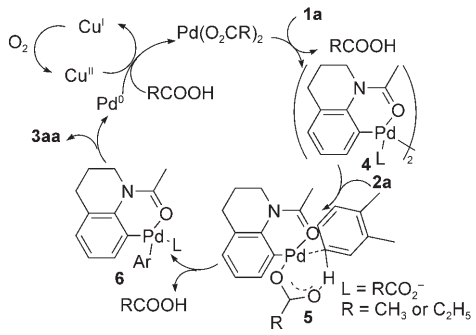


(1)

activation[13] and by steric effects in the second C–H activation.[14] To further verify our prediction, the more sterically hindered *p*-xylene was subjected to this transformation, and *ortho* arylation was observed in very low yield, with most of the starting material **1a** being recovered.

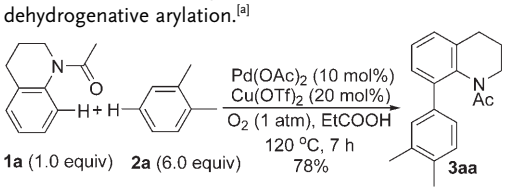


Scheme 2. Proposed catalytic cycle for highly selective cross dehydrogenative arylation (CDA).

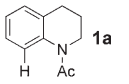
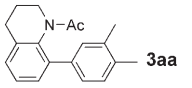
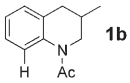
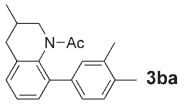
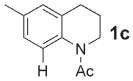
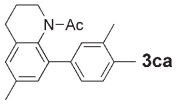
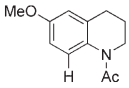
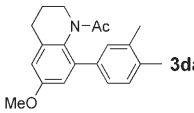
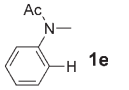
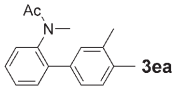
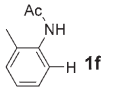
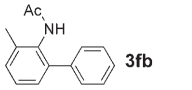
The scope of *N*-acetanilides was further investigated (Table 1). N-Alkylated and free anilines were not fit for this transformation. Different derivatives of *N*-acetyl-1,2,3,4-tetrahydroquinoline, regardless of substitution at the aliphatic or aromatic ring, were perfectly suitable substrates for this transformation (entries 1–4, Table 1). However, *N*-methyl acetanilide **1e** did not serve well as a substrate and quickly decomposed under cross dehydrogenative arylation (CDA) conditions (entry 5, Table 1). Additional studies indicated that acetanilide **1f** was a good substrate, and the N–H bond was not functionalized (entry 6, Table 1). In this case, only the *ortho* sp^2 C–H bond was arylated efficiently.

Furthermore, different common arenes were tested for this *ortho* arylation behavior (Table 2). We found: 1) Less hindered *ortho*- and *meta*-dialkyl-substituted electron-rich benzene derivatives could be utilized as the arene source to perform the *ortho* arylation with excellent selectivities (entries 1 and 3, Table 2). With monoalkyl-substituted arenes, two isomers (functionalized at the *meta* and *para* positions) were isolated as a mixture (entries 4, 5, 7, and 8, Table 2). Thus, steric hindrance rather than electronic effects played the vital role in controlling the selectivity of the second C–H activation. 2) Different arenes with fused rings, even with heteroatoms, could serve as substrates to complete this transformation at less hindered positions (entry 6, Table 2). 3) Benzene could be employed as the arene source with excellent efficiency (entry 6, Table 1; entry 2, Table 2). Even electron-deficient arenes, such as biphenyl and fluorobenzene, were also good reagents for this arylation, but a higher catalyst loading was required (entries 7 and 8, Table 2). The

Table 1: Substrate scope of *N*-acetanilides for Pd-catalyzed cross dehydrogenative arylation.[a]



(1)

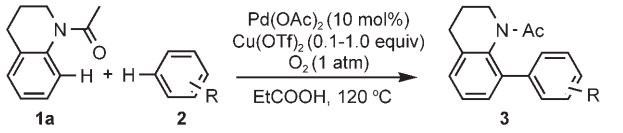
Entry	1	3	Yield [%][b]
1			78 73[c]
2			71
3			86
4			64
5[d]			16
6[e]			66

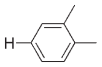
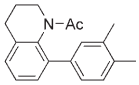
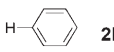
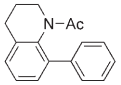
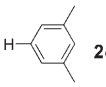
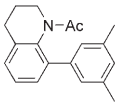
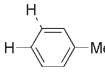
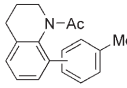
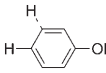
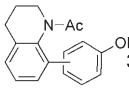
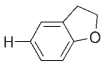
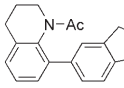
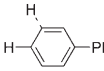
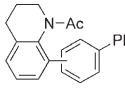
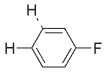
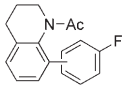
[a] All reactions were performed using **1** (0.3 mmol), **2a** (1.0 mL), and EtCOOH (1.5 mL) unless noted otherwise (see the Supporting Information). [b] Yields of isolated product. [c] Yield of isolated product on a scale of 10.0 mmol. [d] Most of starting material **1e** decomposed under these conditions. [e] Benzene (1 mL) was used in place of **2a**.

reactivity of these electron-deficient arenes seems to support the proton-abstraction pathway to activate the C–H bond of a second arene to afford intermediate **6** via **5**, as described in the aforementioned catalytic cycle (Scheme 2).[15]

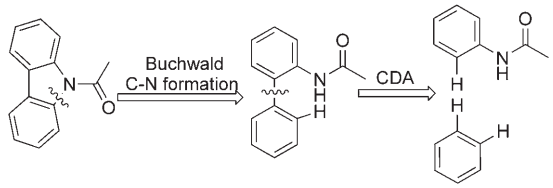
Carbazole and its derivatives further drew our attention, as they are the key structural units in many natural drugs and synthetic optical materials.[16] On the basis of the new observations, we aimed to construct the carbazole unit through a process free of halogenated and metal-containing reagents (Scheme 3). In our design, the C–N bond of carbazole could be constructed by Pd^{II}-catalyzed C–H activation, as demonstrated by Buchwald and co-workers.[17] The *ortho*-arylated acetanilides could be constructed by our new CDA reaction with commercially available acetanilides and arenes. Building on the above developments, we envisioned that the regioselective *ortho* palladation of acetanilides would give a palladacycle analogous to **4**. This key intermediate may undergo further C–H activation of a second arene to construct biaryl C–C bonds, thereby furnishing the intermolecular cross-coupling product. Thus, the carbazole core can be constructed through three C–H and one N–H functionalization with a Pd catalyst in a highly chemo- and regioselective manner. Prefunctionalization of arenes with

Table 2: Cross dehydrogenative arylation of 1,2,3,4-*N*-acetyltetrahydroquinoline **1a** with different arenes.[a]



Entry	Arene **2**	**3**	Yield [%][b]
1	 **2a**	 **3aa**	78 73[c]
2	 **2b**	 **3ab**	66
3	 **2c**	 **3ac**	46
4[d]	 **2d**	 **3ad+3ad'**	78 (1.1:1)
5[d]	 **2e**	 **3ae+3ae'**	69 (2.5:1)
6[e]	 **2f**	 **3af**	63
7[d,f]	 **2g**	 **3ag+3ag'**	43 (1:1)
8[g,h]	 **2h**	 **3ah+3ah'**	48 (2.3:1)

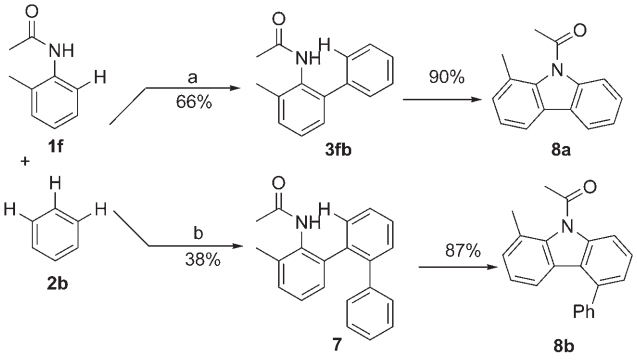
[a] All reactions were carried out using **1a** (0.3 mmol), **2** (1.0 mL), EtCOOH (1.5 mL), and the appropriate amount of of $Cu(OTf)_2$ (see the Supporting Information for details). [b] Yield of isolated product. The ratios given in parenthesis refer to the relative yield of *para*- to *meta*-substituted product. [c] Yield of isolated product on a scale of 10.0 mmol. [d] The ratio of the two isomers was determined by GC. [e] Some by-products (less than 10%) were observed, but their structures could not be determined. [f] 5.0 equiv biphenyl was used. [g] 20 mol% $Pd(OAc)_2$ was used. [h] The ratio of the two isomers was determined by ^1H NMR spectroscopy.



Scheme 3. A rational design on construction of carbozoles through multiple C–H activations by Pd catalysis avoiding organohalides and organometallic reagents.

halide and boronic acids can thus be avoided in this efficient synthetic scheme.

We tested the synthesis of the carbazole scaffold with multiple C–H activation steps, as envisioned. Under the standard arylation conditions, *ortho*-phenylated acetanilide **3fb** was produced in a good yield (Scheme 4). This compound could be directly transformed into carbazole **8a** (isolated in 91% yield) under Buchwald conditions. Starting from **1f**, the *ortho* position of the newly installed phenyl ring of **3fb** could

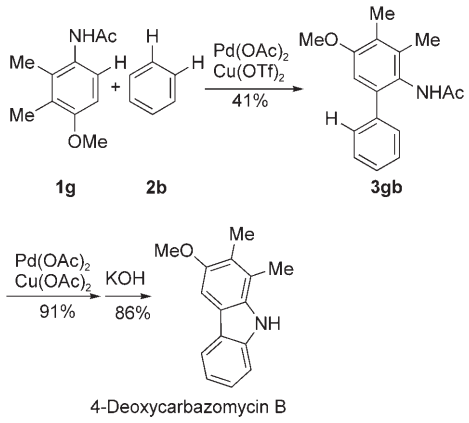


Scheme 4. Pathways completely free of halogenated and organometallic reagents for the synthesis of polysubstituted carbozoles through multiple C–H activations. a) Benzene (1 mL), **1f** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), and $Cu(OTf)_2$ (1 equiv) in propionic acid (1.5 mL), 4–6 h. b) Benzene (1.0 mL), **1f** (0.3 mmol), $Pd(OAc)_2$ (20 mol%), and $Cu(OTf)_2$ (1 equiv) in propionic acid (1.5 mL), 6 h.

be further phenylated to produce acetanilide **7** through a second CDA reaction by simply increasing the catalyst loading under the same conditions. Carbazole **8b** was easily obtained from **7** through the Pd^{II}-catalyzed C–N bond formation in an excellent yield and high selectivity and could undergo a third cross-coupling to yield derivatives.

With simple processes completely free of halogenated and organometallic reagents, 4-deoxycarbazomycin B, a degradation product of the natural product carbazomycin B, was synthesized in few simple steps (Scheme 5).[18] This methodology allowed the swift development of a diverse library of carbazoles with different functionalities from commercially available acetanilides and common arenes.

In conclusion, our new concept was realized to conduct highly selective cross-coupling of arenes controlled by directing groups, and a practical method was developed to



Scheme 5. Synthesis of 4-deoxycarbazomycin B from substituted acetanilide and benzene through sequential C–H activation.

regioselectively form aryl–aryl bonds in a very efficient and environmentally benign manner. These transformations included two different steps to activate two different kinds of inert aromatic C–H bonds. The regioselectivity of this cross-coupling was controlled by directing groups during the first step and by steric hindrance during the second step. This method could be utilized in multiple steps to construct fully functionalized carbazole derivatives, in which different types of C–H bonds could be functionalized under mild conditions. We showed that five arene C–H bonds could be activated in unprecedented sequential transformations to construct complicated structures. The development reported herein offers a process completely free of halogenated and organometallic reagents to make organic molecules with simple starting materials.

Experimental Section

Cross dehydrogenative arylation (CDA) of *N*-acetanilides with arenes: All reactions were performed on a 0.3-mmol scale relative to **1**. $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $Cu(OTf)_2$ (22.0 mg, 0.06 mmol), and *N*-acetyl-1,2,3,4-tetrahydroquinoline **1a** (52.5 mg, 0.3 mmol) were weighed in air and added to an oven-dried 25-mL Schlenk tube. The septum-sealed tube was evacuated and refilled with O_2 three times. EtCOOH (1.5 mL) and *o*-xylene **2a** (191.0 mg, 1.8 mmol) were added, and the mixture was stirred at 120 °C under oxygen (1 atm) until the substrate was completely consumed. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (80 mL). The organic phase was washed with water (2×30 mL) and saturated Na_2CO_3 (30 mL) and dried over $MgSO_4$. The solvent was removed, and the residue was subjected to flash column chromatography with ethyl acetate/petroleum ether (1:10) as eluent to obtain the desired product **3aa** (65.0 mg, 78 % yield).

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