C–H Activation

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Indoles from Simple Anilines and Alkynes: Palladium-Catalyzed C–H Activation Using Dioxygen as the Oxidant**

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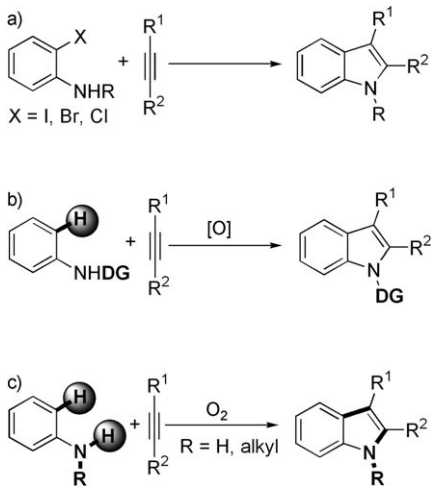
Indoles are ubiquitous bioactive heterocycles in nature.[1] Their importance in medicinal chemistry has stimulated considerable interest from organic chemists, and has encouraged the development of new synthetic strategies to prepare these compounds.[2] In the past decades, transition-metal-catalyzed intermolecular cyclizations of *ortho*-halogenated anilines with internal alkynes have emerged as a powerful method for constructing indoles (Scheme 1a).[3] However, *ortho*-halogenated anilines are required and halide byproducts are produced in these methods. The C–H functionalization approach has received substantial attention because of its sustainable and environmentally benign features.[4] In this regard, preactivated intramolecular cyclization by C–H activation presents one of the most exciting and significant methods.[5] Very recently, in contrast to the requirement of the substrate preactivation procedure, Glorius et al.[6] described a one-pot indole synthesis from aniline and methyl acetoacetate involving an $InBr_3$-catalyzed condensation and a $Pd(OAc)_2$-catalyzed oxidative cyclization. Moreover, Fagnou and coworkers[7a] reported a significant rhodium-catalyzed intermolecular cyclization between alkynes and *N*-acetyl anilines, in which the acetyl species functioned as a directing group,[8,9] assisting in the C–H activation (Scheme 1b). Despite the significant advance, directing groups are required for the intermolecular approach. The direct approach from simple and readily available anilines by C–H activation remains a challenging task (Scheme 1c).

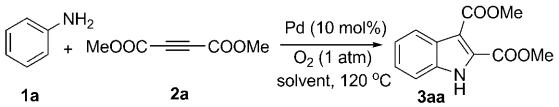


Scheme 1. Strategies involving C–H activation for the preparation of indoles. a) Type 1: Cyclization with *ortho*-halogenated anilines. b) Type 2: Directing group (**DG**) assisted approach. c) Type 3: Direct approach from simple anilines.

Furthermore, the oxidant plays an essential role in the catalytic cycle of C–H activation. Although oxidants such as $Cu(OAc)_2$, AgOAc, $PhI(OAc)_2$, BQ etc. have been proven to be excellent and practical,[4–9] dioxygen is an ideal oxidant and offers attractive industrial prospects in terms of green and sustainable chemistry.[10,11] Herein, we demonstrate the first efficient and direct approach to indoles from simple and readily available anilines and alkynes by using C–H activation catalyzed by $Pd(OAc)_2$ and O_2 as the oxidant (Scheme 1c).

Initially we focused on the direct synthesis of the indole from simple aniline (**1a**) and dimethyl butynedioate (**2a**) through C–H activation in the presence of $Pd(OAc)_2$ in DMSO under 1 atmosphere of O_2. Under these conditions, the desired product **3aa** was observed in 18% yield (Table 1, entry 1). Gratifyingly, 62% of **3aa** was achieved when DMA was employed as the solvent (Table 1, entry 2). Considering

Table 1: Direct indole synthesis from **1a** and **2a** by C–H activation.[a]



1a 2a 3aa

Entry	Catalyst	Solvent	*t* [h]	Yield of **3aa** [%][b]
1	$Pd(OAc)_2$	DMSO	40	18
2	$Pd(OAc)_2$	DMA	40	62
3	$Pd(TFA)_2$	DMA	40	45
4	$Pd(OAc)_2$	PivOH	12	34
5	$Pd(OAc)_2$	DMA/AcOH (4:1)	12	73
6	$Pd(OAc)_2$	DMA/PivOH (4:1)	12	85
7[c]	$Pd(OAc)_2$	DMA/PivOH (4:1)	12	60

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), in solvent (1.25 mL), 1 atm of O_2. [b] Yield of isolated products. [c] The reaction was carried out under air. DMSO = dimethyl sulfoxide, DMA = *N*,*N*-dimethylacetamide, TFA = trifluoroacetate, Piv = pivaloyl.

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that a proper oxidant is essential for fulfilling the catalytic cycle, other organic and inorganic oxidants such as $PhI(OAc)_2$ and $Cu(OAc)_2$ were evaluated, but they resulted in lower yields. Attempts to use other palladium catalysts, such as $Pd(TFA)_2$, $PdCl_2$, and $Pd(PhCN)_2Cl_2$, were also not very successful (Table 1, entry 3; see also Table S1 in the Supporting Information). Additional studies indicated that the addition of a base or a Lewis acid such as AgOTf or $In(OTf)_3$ decreased the yield of **3aa** (see Table S1). Although the efficiencies were low when the reaction was carried out in acids such as PivOH (Table 1, entry 4; see also Table S1), the yields dramatically increased when using a mixture of DMA and an acid as the solvent (Table 1, entries 5 and 6). We believed that the acid would serve as a proton shuttle and assist in the transformation.[12] Notably, the best solvent system for this transformation was the mixture of DMF and PivOH (4:1) (Table 1, entry 6). Interestingly, a 60% yield was achieved by using air as the oxidant instead of O_2 (Table 1, entry 7).

Under the optimal reaction conditions, different anilines were surveyed (Figure 1). Reactions of anilines having electron-withdrawing or electron-donating groups proceeded efficiently with moderate to excellent yields (38–99%; Figure 1). All *para*-, *meta*-, and *ortho*-substituted anilines were smoothly transformed into the desired products, which indicated that steric bulk did not significantly affect the reactivity. When anilines were substituted at the *meta* position, the products resulting from reaction at the more sterically accessible position (e.g., **3ca** and **3ea**) were regioselectively obtained. Notably, functionalized anilines underwent the reaction, leading to chloro- and hydroxy-substituted indoles (**3oa** and **3pa**); these products could be used in additional transformations. Intriguingly, when 4,4′-oxydianiline was used as the substrate two indole structures were generated, leading to **3ra** in 87% yield.

The scope of the intermolecular cyclization reaction was additionally expanded to a variety of internal alkynes (Table 2). Electron-deficient alkynes were tolerated for this transformation. Notably, aryne **2e** smoothly underwent cyclization leading to carbazole **3ae** in 60% yield (Table 2, entry 5). 2-Phenyl-3-cyano-*1H*-indole (**3ad**) was formed in 20% yield by the initial amination at the electron-deficient position of the alkyne (Table 2, entry 4).

Notably, N-monosubstituted anilines performed very well, affording the corresponding indoles (Table 2, entries 6–8).

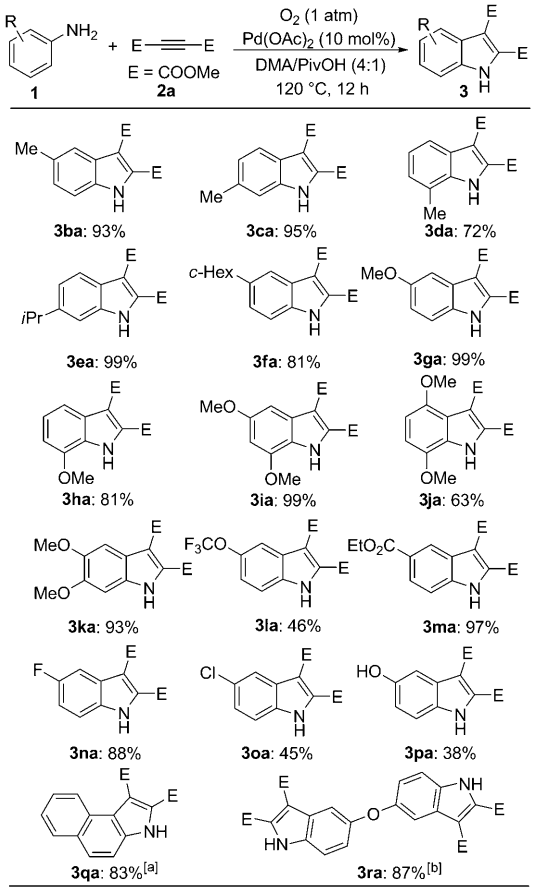
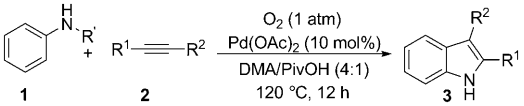
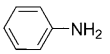
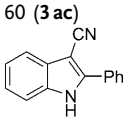
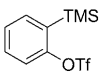
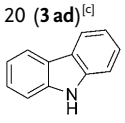
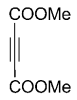
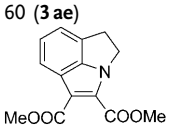
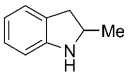
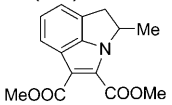
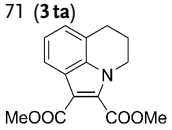


Figure 1. Palladium-catalyzed intermolecular cyclization of **2a** with different anilines. Reaction conditions: **1** (0.48 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (0.04 mmol), in solvent (2.5 mL), 1 atm of O_2, 120°C, overnight; yield of the isolated product shown. [a] The ratio of the substituted 3*H*-benz[*e*]indole to 1*H*-benz[*f*]indole is 12:1. [b] **2a** (3.0 equiv) and $Pd(OAc)_2$ (20 mol%) were used.

Table 2: Palladium-catalyzed intermolecular cyclization of **1** with different internal alkynes.[a]

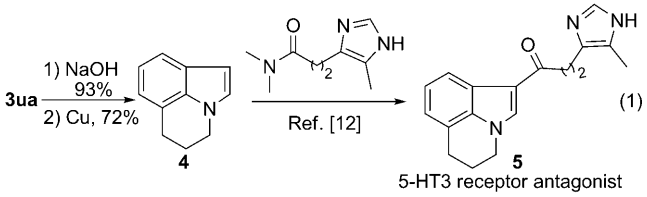


Entry	1	2	Yield of 3 [%][b]
1		$R^1 = R^2 =$ COOMe (**2a**)	85 (**3aa**)
2		$R^1 = R^2 =$ COOEt (**2b**)	75 (**3ab**)
3	**1a**	$R^1 = R^2 =$ COO*i*Pr (**2c**)	60 (**3ac**)
4			
	1a	**2d**	20 (**3ad**)[c]
5			
	1a	**2e**	60 (**3ae**)
6			
	1s	**2a**	46 (**3sa**)[c]
7			
	1t	**2a**	71 (**3ta**)
8			
	1u	**2a**	83 (**3ua**)

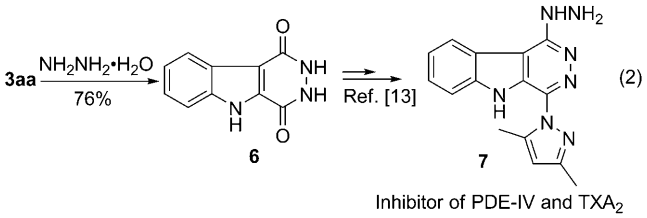
[a] Reaction conditions: **1a** (0.48 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (0.04 mmol), in solvent (2.5 mL), 1 atm of O_2, 120°C, overnight. [b] Yield of isolated product. [c] The low yield was a result of the incomplete conversion of the enamine intermediates **8** [see Eq. (2)] into the desired product.

When 2,3-dihydro-indole (**1s**) was used as the substrate in this transformation, the 1,7-five-membered annulated indole **3sa** was obtained in 46% yield; the low yield is attributable to the effect of the strain of two five-membered rings. Intriguingly, the yield was increased to 71% when a methyl group was present at the 2-position (Table 2, entry 7). Moreover, the 1,7-six-membered annulated indole **3ua** was generated in 83% yield (Table 2, entry 8).

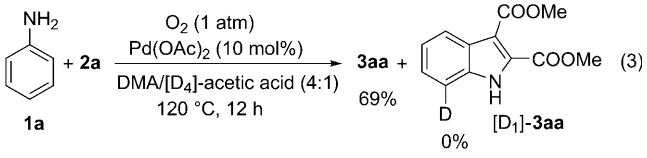
This transformation provides many opportunities for applications to organic synthesis. The corresponding unfunctionalized indole derivatives (**4**) could be easily generated by hydrolysis and copper-mediated decarboxylation of the products **3** and then additionally manipulated to give the 1,7-annulated indole derivative **5** [Eq. (1)]; **5** is a high-affinity 5-HT_3 receptor antagonist,[13] which can be easily prepared in



only four steps from readily available 1,2,3,4-tetrahydroquinoline (**1u**) via **3ua** by using our method. Also, **7**, an inhibitor of PDE-IV and TXA_2,[14] could be synthesized from **3aa** via **6** [Eq. (2)].

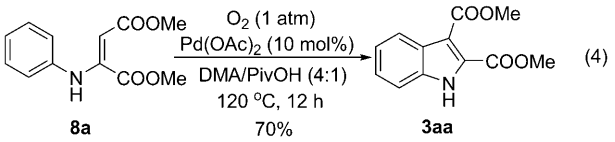


To probe the reaction mechanism, the reaction of **1a** and **2a** was tested using a mixture of DMA and [D_4]-acetic acid (4:1) as the solvent. [D_1]-**3aa** was not detected [Eq. (3)],

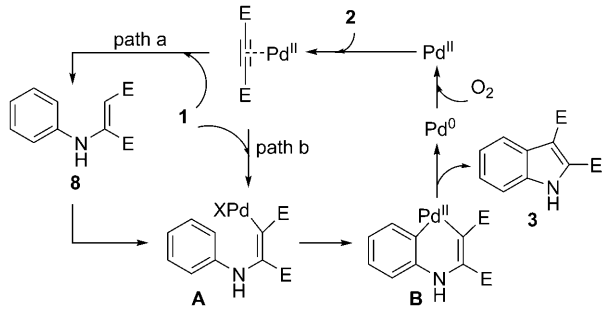


which indicates that the C–H activation is not reversible. In addition, **8a** was detected by using GC methods to monitor the reaction of **1a** and **2a**. We next tested the reaction of **8a** under the standard reaction conditions, and **3aa** was formed in 70% yield from **8a** [Eq. (4)], which indicates that **8a** could be a potential intermediate in the transformation.

On the basis of these preliminary results, the catalytic cycle of this transformation was hypothesized as shown in

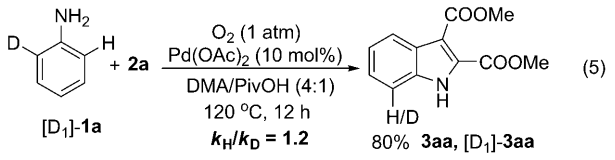


Scheme 2. Alkyne **2** is initially activated by palladium(II) which acts as a Lewis acid,[15] and subsequent hydroamination leads to enamine **8** (Scheme 2, path a). Then the electrophilic



Scheme 2. Proposed mechanism for the transformation.

palladation of **8** and deprotonation[16] produce the intermediate **A** (Scheme 2, path a). Alternatively, aminopalladation[17] of alkyne **2** could occur to form the intermediate **A** (Scheme 2, path b), which generates the intermediate **B** by an acid-promoted electrophilic aromatic palladation and subsequent proton abstraction.[12a,b] The intermediate **B** then undergoes reductive elimination to give the expected product. The resulting palladium(0) is additionally oxidized to palladium(II) by O_2 to complete this catalytic cycle. The intramolecular isotope effect study ($k_H/k_D = 1.2$) provides additional evidence to support the assumed electrophilic aromatic palladation pathway [Eq. (5)].



In conclusion, we have discovered a unique and direct approach for constructing indoles from simple and readily available anilines and alkynes by C–H activation. O_2 (1 atm) is used as the oxidant in this catalytic cycle. Through this method, both N-nonsubstituted and N-alkyl monosubstituted anilines can be successfully transformed into the corresponding indoles. These reaction conditions are mild and do not require the addition of a ligand or base. Studies are ongoing in our laboratory to understand the reaction mechanism and discover synthetic applications.

Experimental Section

Dimethyl 1H-indole-2,3-dicarboxylate (**3aa**):[18] $Pd(OAc)_2$ (4.5 mg, 10 mol%) was added to a 20 mL Schlenk tube, and the tube was then

purged three times with O_2. Subsequently, aniline **1a** (22.0 μL, 0.24 mmol), dimethyl butynedioate **2a** (24.6 μL, 0.20 mmol), and DMA/PivOH (4:1 v/v; 1.25 mL) were added. The reaction mixture was gradually heated from RT to 120 °C under O_2 (1 atm) and stirred for 12 h during which it was monitored by TLC. The solution was then cooled to RT, diluted with ethyl acetate (30 mL), washed with H_2O (3×10 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 5:1) to afford 39.5 mg (85 %) of **3aa**: white solid; Mp: 104–106 °C (*n*-hexane/ethyl acetate); IR: (KBr): $\tilde{\nu}_{max} = 3305$, 1728, 1690, 1281, 1259, 1068, 752 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) $\delta = 9.48$ (brs, 1H), 8.06 (d, $J = 7.8$, 1H), 7.46–7.25 (m, 3H), 3.99 (s, 3H), 3.98 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$): $\delta = 164.6$, 161.4, 134.8, 128.0, 126.8, 125.9, 122.7, 122.6, 111.9, 52.7, 51.8 ppm; MS (70 eV): *m/z* (%): 233.1 (39) $[M]^+$, 143.0 (100).

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