Cycloaromatization

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A Palladium-Catalyzed Oxidative Cycloaromatization of Biaryls with Alkynes Using Molecular Oxygen as the Oxidant**

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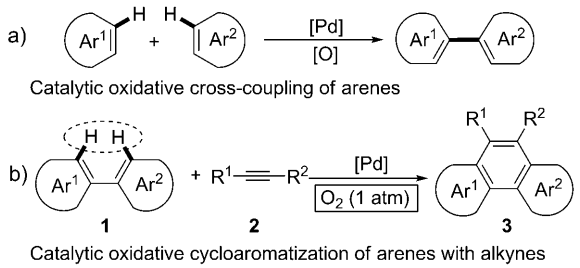
Polycyclic aromatic hydrocarbons (PAHs) have attracted considerable attention not only because of their remarkable biological and pharmacological activity,[1] but also because of their electrochemical and photochemical properties.[2] Numerous synthetic methodologies for the construction of these polycyclic aromatic systems have been developed in the past decades,[3] among which, the palladium-catalyzed annulation of alkynes by functionally substituted aromatics has been particularly effective for the synthesis of a wide variety of carbocycles and heterocycles.[4] Recently, the functionalization of C–H bonds using directing groups has presented an attractive and powerful strategy for the generation of heteroaromatic compounds, such as indoles, isoquinolines, carbazoles, benzothiazoles, and pyridines.[5] However, the cycloaromatization of alkynes with arenes through activation of a C–H bond to form benzene rings still poses a challenge.[6] A major advance in this area has been the polycyclic aromatic synthesis described by Miura et al.[6a] This progress was achieved through rhodium-catalyzed annulation of phenylazoles with internal alkynes through dual cleavage of C–H bonds directed by an *ortho*-azole group using $Cu(OAc)_2$ as the oxidant. However, the requirement of a directing group and a copper oxidant may limit its applications. Herein, we describe the first palladium-catalyzed cycloaromatization of biaryls with alkynes through dual activation of C–H bonds using O_2 as the oxidant (Scheme 1).

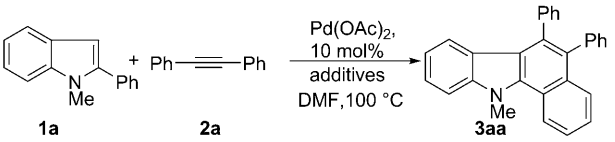
In 2007, Stuart and Fagnou reported a significant cross-coupling reaction of unactivated arenes that was catalyzed by Pd^{II} in the presence of $Cu(OAc)_2$ as the oxidant (Scheme 1a).[7] Very recently, our research group has developed a palladium-catalyzed synthesis of indoles[8] using O_2 as the oxidant.[9] We envisioned that C–H activation of biaryls may occur through a relay-type action involving an internal alkyne to achieve the cycloaromatization, thus leading to fluorescent polycyclic aromatic compounds (Scheme 1b).



Scheme 1. a) Direct cross-coupling between two arenes. b) Cycloaromatization reaction through the activation of C–H bonds between biaryls and alkynes.

With this hypothesis in mind, we initially focused on diphenylacetylene (**2a**) with 1-methyl-2-phenyl-1*H*-indole (**1a**), which would induce cleavage of the C–H bond at C3 by a Friedel–Crafts-type process utilizing electrophilic metal catalysts.[7,10] Gratifyingly, the desired 11-methyl-5,6-diphenyl-11*H* benzo[a]carbazole (**3aa**) was formed in 45% yield by using $Pd(OAc)_2$ as the catalyst and O_2 (1 atm) as the oxidant in DMF (Table 1, entry 1). Other oxidants such as $Cu(OAc)_2$, Ag_2CO_3, $PhI(OAc)_2$, or BQ gave low yield (see the Supporting Information). After extensive screening of different parameters (Table 1 and the Supporting Information), the optimum reaction conditions were determined: $Pd(OAc)_2$ (10 mol%), K_2CO_3 (0.3 equiv), TBAB (0.5 equiv), PivOH (1.0 equiv), DMF, O_2 (1 atm), 100 °C, 12 h, under which, the highest yield (84%) was achieved (Table 1, entry 3). Signifi-

Table 1: Palladium-catalyzed cycloaromatization of **1a** with alkyne **2a**.[a]



Entry	Oxidant (1 atm)	PivOH (equiv)	TBAB (equiv)	K_2CO_3 (equiv)	Yield of **3aa** [%][b]
1	O_2	1.0	–	0.3	45
2	O_2	–	0.5	0.3	35
3	**O_2**	**1.0**	**0.5**	**0.3**	**84**
4	air	1.0	0.5	0.3	54

[a] Standard reaction conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), $Pd(OAc)_2$ (0.02 mmol), K_2CO_3 (0.06 mmol), TBAB (0.10 mmol), PivOH (0.20 mmol), DMF (2 mL), 100 °C, O_2 (1 atm), 12 h. [b] Yield of isolated product. DMF = *N*,*N*-dimethylformamide, Piv = pivaloyl, TBAB = tetra-*n*-butylammoniumbromide.

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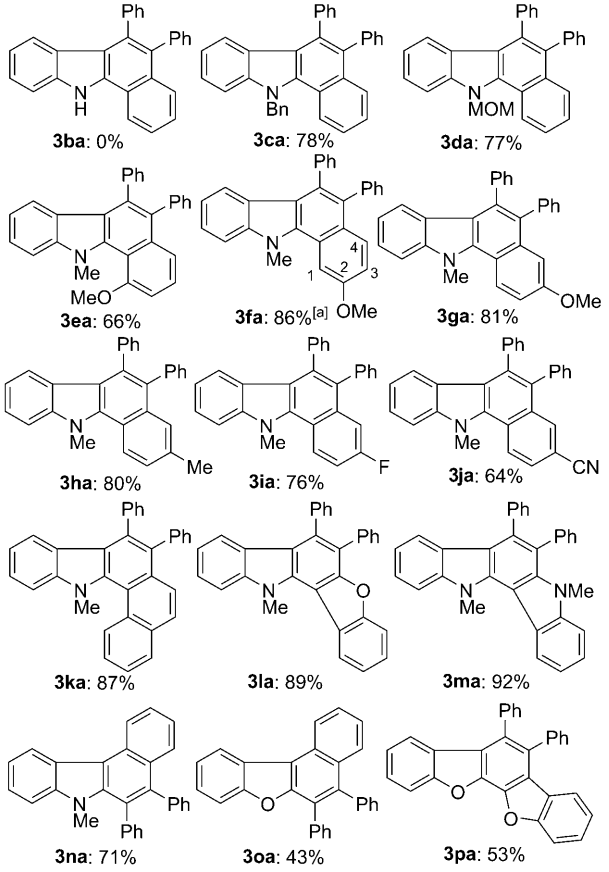
cantly, a 54% yield was achieved even when using air as the oxidant instead of O_2 (compare Table 1, entries 3 and 4).

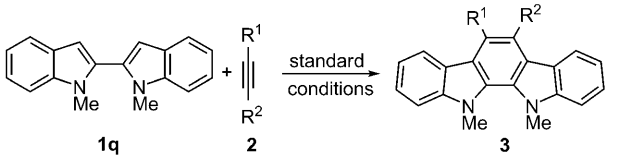
Under these optimized reaction conditions, protecting groups such as Bn and MOM were well tolerated to give **3ca** and **3da**, respectively (Scheme 2). Notably, both electron-donating (*para*-, *meta*-, and *ortho*-substituted) and electron-withdrawing substrates could be smoothly transformed into the desired products in good yields (**3ea**–**3ja**, 64–86%). Furthermore, the larger aromatic biaryl substrates (Ar^2 = naphthalen-1-yl, benzofuran-3-yl, 1-methyl-1*H*-indol-3-yl) proceeded in excellent yields (**3ka**–**3ma**, 87–92%), which indicated that the steric and electronic effect of biaryls did not significantly affect the reactivity. Notably, 3-arylindole could also induce cleavage of the C–H bond at C2 (**3na**, 71%). Intriguingly, the strategy was also applicable to the annulation of other biaryl compounds, such as 3-phenylbenzofuran and 2,2′-bibenzofuran to give **3oa** and **3pa**, respectively.

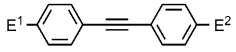
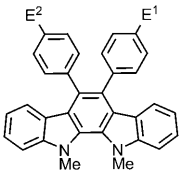
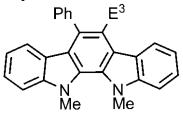
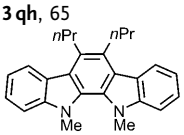


Scheme 2. Palladium-catalyzed cycloaromatization of **1** with alkyne **2a**. Standard reaction conditions: **1** (0.20 mmol), **2a** (0.30 mmol), $Pd(OAc)_2$ (0.02 mmol), K_2CO_3 (0.06 mmol), TBAB (0.10 mmol), PivOH (0.20 mmol), DMF (2 mL), 100 °C, O_2 (1 atm), 12 h. Yields are of isolated products. [a] 2-OMe/4-OMe = 56:44, the ratio of the regioisomers was determined by ^1H NMR spectroscopy. Bn = benzyl, MOM = methoxymethyl.

To investigate the scope of the internal alkyne, 2,2′-bis(*N*-methylindolyl) was chosen as the substrate in view of the interesting biological properties displayed by numerous natural products incorporating the indolo[2,3-*a*]carbazole skeletons. These results indicated that most diarylacetylenes with electron-withdrawing and electron-donating groups proceeded efficiently (60–90%; Table 2, entries 1–6). Markedly, dialkynes also underwent the reaction despite of their bulkiness (Table 2, entries 6 and 8). Moreover, alkyl-substituted alkynes such as 1-phenyl-1-hexyne (**2g**) and oct-4-yne (**2i**) were converted into **3qg** and **3qi** in moderate yields, respectively (Table 2, entries 7 and 9).

Table 2: Palladium-catalyzed cycloaromatization of **1q** with alkynes **2**.[a]

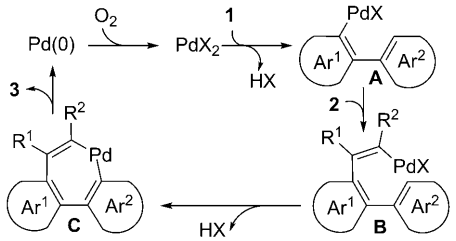


Entry	Alkyne	Product, yield of **3** [%][b]
		
1	**2a**, $E^1 = E^2 = H$	**3qa**, 87
2	**2b**, $E^1 = E^2 = OMe$	**3qb**, 63
3	**2c**, $E^1 = E^2 = CF_3$	**3qc**, 68
4	**2d**, $E^1 = E^2 = Cl$	**3qd**, 79
5	**2e**, $E^1 = H$; $E^2 = NO_2$	**3qe**, 90
6	**2f**, $E^1 = H$; $E^2 = Ph–C\equiv C$	**3qf**, 60
		
7	**2g**, $E^3 = n$Bu	**3qg**, 61
8	**2h**, $E^3 = Ph–C\equiv C$	**3qh**, 65
		
9	**2i**	**3qi**, 73

[a] Standard reaction conditions: **1q** (0.20 mmol), **2** (0.30 mmol), $Pd(OAc)_2$ (0.02 mmol), K_2CO_3 (0.06 mmol), TBAB (0.10 mmol), PivOH (0.20 mmol), DMF (2 mL), 100 °C, O_2 (1 atm), 12 h. [b] Yield of isolated product.

A plausible mechanism for the reaction of **1** with alkyne **2** is illustrated in Scheme 3. The initiated electrophilic aromatic palladation[7,10] affords a Pd^{II} intermediate **A**, and appears to be the key process for the cycloaromatization. The resulting intermediate **A** subsequently inserts into alkyne **2** to produce a vinylic palladium(II) intermediate **B**, which is suitable for acid-promoted electrophilic aromatic palladation and subsequent proton abstraction[11] to afford a seven-membered palladacycle **C**.[12,13c] Subsequent reductive elimination generates the cyclic product as well as a Pd^0 complex that can be reoxidized to the Pd^{II} species by O_2 (1 atm; Scheme 3).

With the **3aa**–**3pa** and **3qa**–**3qi** in hand, a preliminary survey of their optical properties was carried out.[13] The photophysical properties of **3aa** and **3qa** (as the representa-



Scheme 3. Plausible mechanism for the reaction of **1** with **2**.

tive examples) are outlined in Figure 1 and Table 3 (for the photophysical properties of the other products **3**, see the Supporting Information). The absorption bands of these

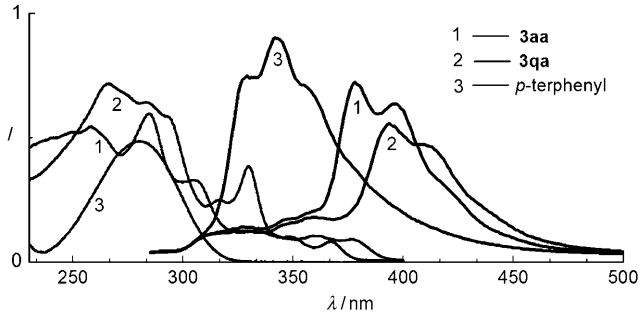


Figure 1. Absorption spectra (——) and luminescence spectra (——) of **3aa**, **3qa**, and *p*-terphenyl in CH_2Cl_2.

Table 3: Optical properties of **3aa** and **3qa**.[a]

Compounds	λ_{abs} [nm] (log ε)	λ_{em} [nm]	Φ_f[b]
3aa	258 (4.56), 285 (4.60), 305 (4.34)	378, 397	0.57
3qa	266 (4.68), 329 (4.41)	394, 408	0.35

[a] CH_2Cl_2 was used as the solvent for the UV/Vis ($c = 1.5\times10^{-5}$ M) and fluorescence ($c = 1.5\times10^{-6}$ M) spectra. [b] Determined by comparison with a solution of *p*-terphenyl in CH_2Cl_2 excited at 265 nm.

products appear in the region of 250 to 350 nm: depending on the electron-donating or electron-withdrawing ability of the substituent groups. In CH_2Cl_2 solution, these compounds exhibit fluorescence ranging from 370 to 420 nm with quantum efficiencies (Φ) ranging from 0.29 to 0.58. It is observed that the fluorescence efficiencies of the unsymmetrical substrates are consistently higher than those of the symmetrical substrates.

In conclusion, we have demonstrated the first palladium-catalyzed cycloaromatization of 2- and 3-arylindoles (as well as 2- and 3-arylbenzofurans) with internal alkynes through dual activation of C–H bonds. Molecular oxygen (1 atm) was used as the oxidant in this catalytic cycle. The reaction outcomes not only provide a new strategy for constructing aromatic compounds from biaryls and internal alkynes, but also offers an efficient approach for the preparation of synthetically and medicinally important polycyclic carbazoles. Furthermore, some of the resulting polycyclic heteroaromatics exhibit intense fluorescence. Further studies to gain an in-depth understanding of the mechanism and the synthetic applications of this reaction are ongoing in our laboratory.

Experimental Section

Synthesis of 11-Methyl-5,6-diphenyl-11*H*-benzo[a]carbazole (**3aa**): $Pd(OAc)_2$ (9.0 mg, 10 mol%), K_2CO_3 (16.6 mg, 30 mol%), TBAB (64.5 mg, 0.5 equiv), PivOH (41.0 mg, 1.0 equiv), **1a** (82.8 mg, 0.40 mmol), **2a** (106.8 mg, 0.30 mmol) were added to a 20 mL Schlenk tube. The tube was purged with O_2 three times before DMF (3.0 mL) was added. The reaction mixture was stirred at 100 °C under O_2 (1 atm) for 12 h and was monitored by TLC. The solution was then cooled to RT, diluted with ethyl acetate (40 mL), washed with H_2O (3×10 mL), dried over $MgSO_4$, filtered, and dried under vaccum. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 50:1) to afford **3aa** (128.5 mg, 84%). IR: (KBr) $\tilde{\nu}_{max} = 1442$, 1372, 1330, 1023, 740, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.84$ (d, $J = 8.0$ Hz, 1H), 7.71 (d, $J = 8.4$ Hz, 1H), 7.61 (td, $J = 7.6$, 1.2 Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.46–7.38 (m, 2H), 7.33–7.18 (m, 10H), 6.93 (t, $J = 7.4$ Hz, 1H), 6.66 (d, $J = 8.0$ Hz, 1H), 4.50 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 141.2$, 140.3, 139.6, 135.2, 134.9, 132.8, 131.8, 131.0, 130.2, 128.4, 127.9, 127.5, 126.7, 126.2, 124.8, 124.7, 124.4, 123.2, 122.1, 122.0, 121.9, 119.3, 117.8, 108.7, 34.4 ppm; MS (70 eV): 383.2 (100) $[M]^+$; HRMS (ESI) calcd for $C_{29}H_{22}N$ ($[M+H]^+$): 384.1747; found: 384.1734.

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