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Polyheterocycles by Palladium(II)-Catalyzed Oxidative Domino Reactions Involving Direct C−H Functionalization

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Abstract: A novel palladium(II)-catalyzed oxidative domino reaction sequence of diyne-enones and substituted indoles to afford polyheterocycles involving direct C−H functionalization using air as oxidant has been developed.

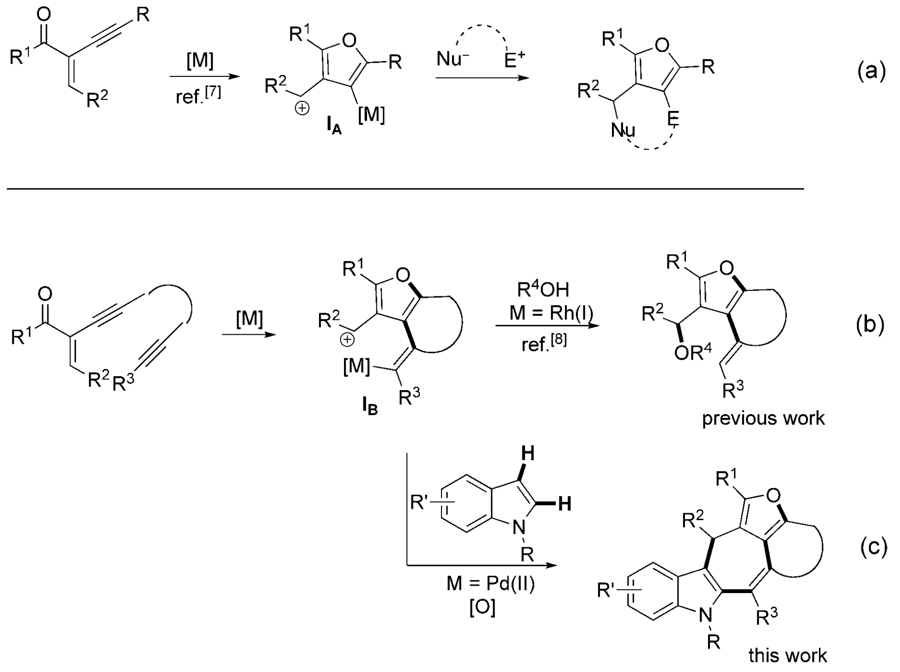
Keywords: air; C−H functionalization; domino reactions; palladium; polyheterocycles; substituted indoles

Highly substituted indoles[1] and furans[2] are two classes of key structural units in many bioactive natural products and building blocks in organic synthesis. Thus, the development of new methods for accessing unique indole and furan derivatives for new leads in drug and material discovery is still highly desirable. The direct C−H functionalization of indoles presents the advantage of convenience and atom economy, which has been applied successfully in the synthesis of indole derivatives.[3] For example, Stoltz,[3a] Shi,[3h] Jiao[3i] and their co-workers have accomplished the direct C−H functionalization of indoles by using environment friendly O_2 or air as oxidant. In contrast to indoles, most C−H functionalizations of furans are known to occur at the 2- or 5-position, the functionalizations at the 3- or 4-position are very difficult,[4a–d] and thus synthesis of highly substituted furans from acyclic precursors has become the predominant way.[4] We report herein a novel palladium(II)-catalyzed oxidative domino reaction[5] by combination of direct C−H functionalization of indoles with cascade cyclizations of diyne-enones using air as the clean oxidant, which provides a rapid access to novel indole-furan polyheterocycles.[6]

Recently, we and others have described a number of catalytic reactions leading to highly substituted furans that involve cationic furanyl-metals $\mathbf{I_A}$ as key reactive intermediates, which were generated from 2-(1-alkynyl)-2-alken-1-ones (yne-enones) in the presence of metal catalysts [Scheme 1, Eq. (a)].[7] As a kind of 1, 3-dipole synthon, $\mathbf{I_A}$ can readily react with nucleophiles and electrophiles[7a–g] or undergo cycloadditions with nitrones[7h] or heterodienes.[7i] Very recently, we reported a Rh(I)-catalyzed tandem reaction of diyne-enones and alcohols leading to 2,3-fused bicyclic furans *via* the corresponding 1,5-dipolar intermediate $\mathbf{I_B}$ [Scheme 1, Eq. (b)].[8] During these studies, we envisaged that indoles may react with $\mathbf{I_B}$ *via* direct C−H functionalization in the presence of palladium(II) species leading to polyheterocycles [Scheme 1, Eq. (c)].

We initiated the palladium-catalyzed domino reaction of diyne-enone **2a** with *N*-methylindole **1a** under different reaction conditions.[9] Gratifyingly, after many attempts, the desired polycyclic product **3aa** was obtained in 85% isolated yield after running the reaction for 18 h at 40 °C in CH_3CN with 6.0 equivalents of *N*-methylindole and 2.0 equivalents of $LiBr{\cdot}H_2O$. There is no difference between air and O_2 as oxidant. Other commonly used oxidants such as CuX_2 (X = Br, Cl), $FeCl_3$, benzoquinone (BQ), and additives such as LiCl and CuX (X = Br, Cl) did not improve the yield. When AgOAc is used as the oxidant, the reaction cannot afford the expected product **3aa**. To our delight, further screening showed that 2.0 equivalents of **1a** and 0.5 equivalent of $LiBr{\cdot}H_2O$ led to a satisfactory yield (standard conditions) [Eq. (1)].

Under these optimized reaction conditions, we next examined the scope and limitations of this transformation *via* variation of indoles (Table 1). The substituent (R′) at the 4-, 5- or 6-position of indole has a



Scheme 1. Previous works and this work.

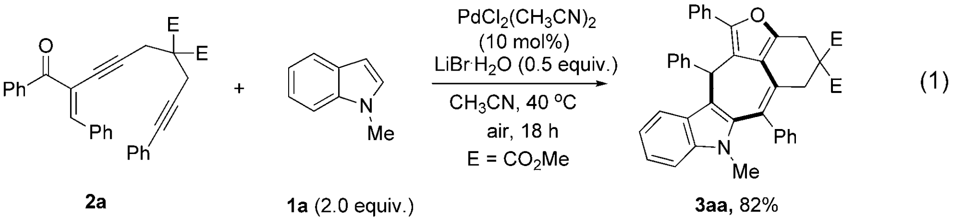
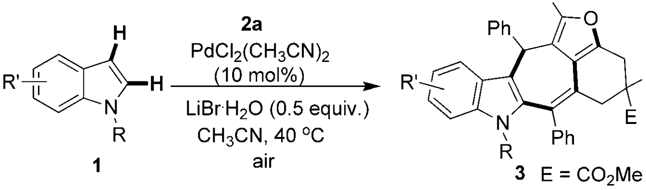


Table 1. Variation of indole components.[a]



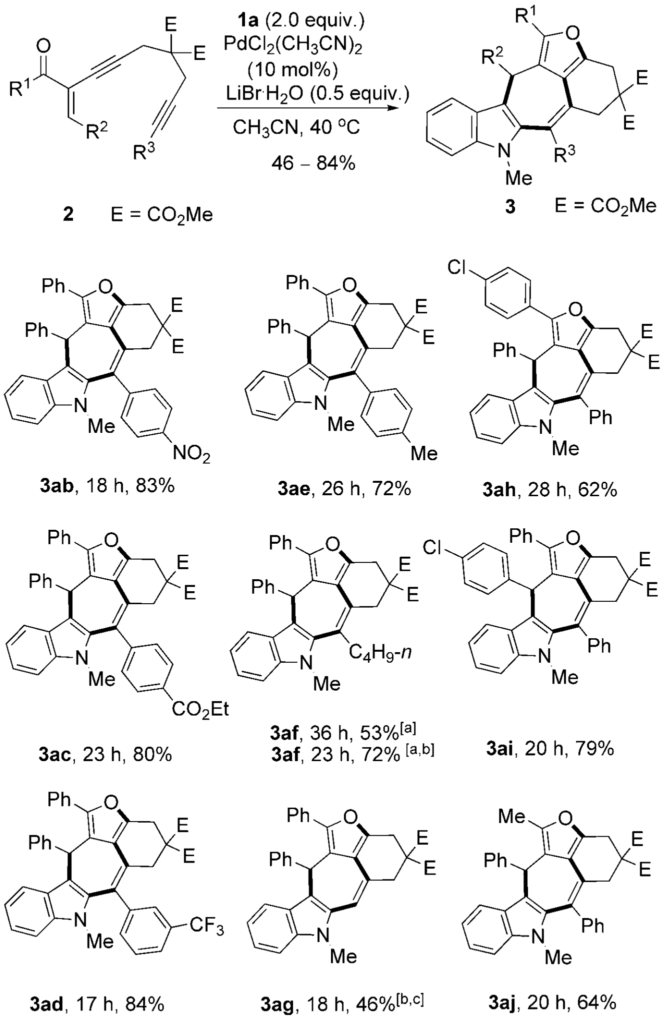
Entry	R′/R (**1**)	Time [h]	Product (Isolated yield [%])
1	H/Me (**1a**)	18	**3aa** (82)
2	5-Me/Me (**1b**)	20	**3ba** (80)
3	5-OMe/Me (**1c**)	18	**3ca** (85)
4	5-Br/Me (**1d**)	22	**3da** (70)
5	6-Me/Me (**1e**)	30	**3ea** (83)
6	H/H (**1f**)	18	**3fa** (69)
7	4-Me/H (**1g**)	18	**3ga** (70)
8[b]	H/Bn (**1h**)	26	**3ha** (72)

[a] All reactions were carried out under the optimal conditions reported in the text, unless otherwisw indicated.

[b] 20 mol% of $PdCl_2(CH_3CN)_2$ were used

little effect on the reaction. Introduction of an electron-donating methoxy group improves the yield a little bit, while the weak electron-withdrawing group (Br) leads to a slightly lower yield (Table 1, entries 3 and 4), indicating that the high nucleophilicity of the indole will help the reaction. The *N*-benzylindole **1h** and the unprotected indole **1f** with an active N–H are also compatible to give the corresponding products in high yields, but the former reaction needs higher catalyst loading to accomplish the reaction (Table 1, entries 6–8).

In general, R^3 at the terminal alkyne moiety of diyne-enones has a significant effect on the yield (Scheme 2). When R^3 is an aryl group, the transformations proceed smoothly to give the corresponding products **3a(b–e)** in high yields, the structure of **3ab** was confirmed by the single-crystal X-ray diffraction analysis.[10] In contrast, when R^3 is an alkyl group, **3af** can be produced in 53% yield under the catalysis of 20 mol% of $[PdCl_2(CH_3CN)_2]$, a higher yield can be achieved with more *N*-methylindole (**1a**, 10 equiv.). However, only a 46% yield of **3ag** is obtained for the diyne-enone with a terminal alkyne ($R^3 = H$), which



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[a] 20 mol% of $PdCl_2(CH_3CN)_2$ was used.

[b] **1a** (10 equiv.).

[c] 15 mol % of $PdCl_2(CH_3CN)_2$ and without LiBr·H_2O.

Scheme 2. Variation of diyne-enone components.

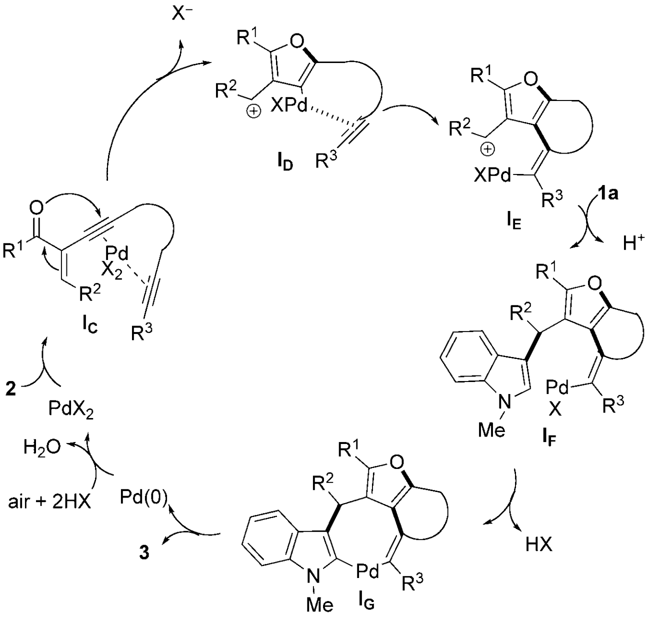
may be caused by the easy oxidative homocoupling of the terminal alkyne under the reaction conditions, LiBr·H_2O was left out in this case in order to accelerate the reaction. R^1 has a little effect on the reaction and an alkyl group can be introduced.

The generality of this transformation was further investigated by employing **2k** with TsN as the tether group and **4** containing a 1, 7-diyne moiety with **1a**, respectively. To our delight, the desired product **3ak** can be obtained in moderate yield [Eq. (2)]. Polycyclic compound **5** with a newly-formed 5,7,7-tricyclic core can be produced in 60% yield under the optimal conditions [Eq. (3)]. Gratifyingly, *N,N*-dimethylaniline **6** can be applied as the nuclophile, leading to a 37% yield of compound **7** [Eq. (4)].

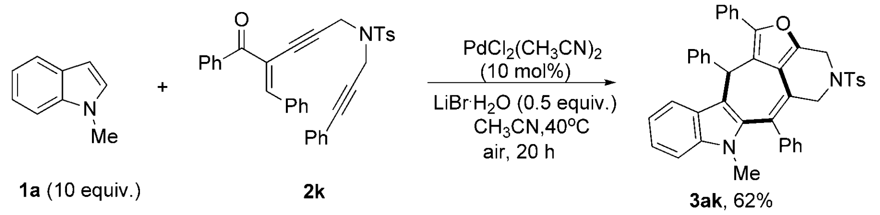
With the polyheterocycle products in hand, a preliminary survey of their optical properties was carried out.[9,11] The absorption bands of these products appear in the region of 250 to 350 nm: depending on the electron-donating or electron-withdrawing ability of substituent groups. In CH_2Cl_2 solution, these compounds exhibit fluorescence ranging from 420 to 450 nm. It is observed that there is a small red shift with substrates containing electron-donating group at the indole.

A plausible mechanism that accounts for this Pd(II)-catalyzed oxidative domino reaction is depicted in Scheme 3. In the presence of LiBr·H_2O, the diyne-enones **2** interacted with PdX_2 or $PdX_2(CH_3CN)_2$ [X = Br or Cl, generated from $PdCl_2(CH_3CN)_2$ and LiBr·H_2O] to give intermediate $\mathbf{I_C}$. The heterocyclization would produce furanyl-palladium $\mathbf{I_D}$ and subsequent *syn*-addition would generate a bicylic vinyl-palladium species $\mathbf{I_E}$ with a carbocation. The nucleophilic addition of **1a** to the carbocation of $\mathbf{I_E}$ at the 3-position of indole would release one proton and give vinyl-palladium species $\mathbf{I_F}$ which would undergo direct C−H activation at the 2-position of indoles to generate a palladacycle $\mathbf{I_G}$ and release the HX. Subsequent reductive elimination would yield the final product and generate a Pd(0) species. An alternative, less possible Heck-like process is insertion of double C−C bond of indole into the vinyl-Pd of $\mathbf{I_F}$, followed by β-H elimination to give the desired product. Pd(0) can be oxidized by the air to regenerate the PdX_2 species in the presence of two molecules of HX.

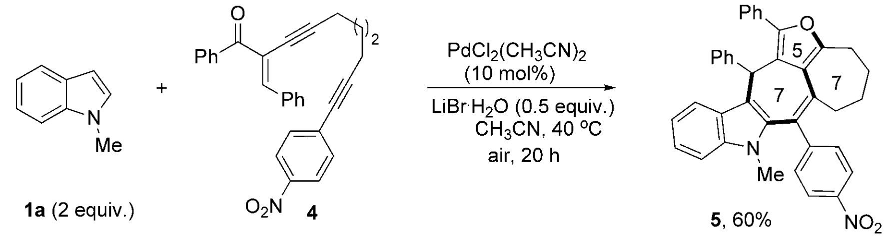
In summary, we have developed a novel palladium(II)-catalyzed oxidative domino reaction of diyne-enones with indoles or *N, N*-dimethylaniline involving direct C−H functionalization, leading to a series of polyheterocyclic compounds with three newly formed



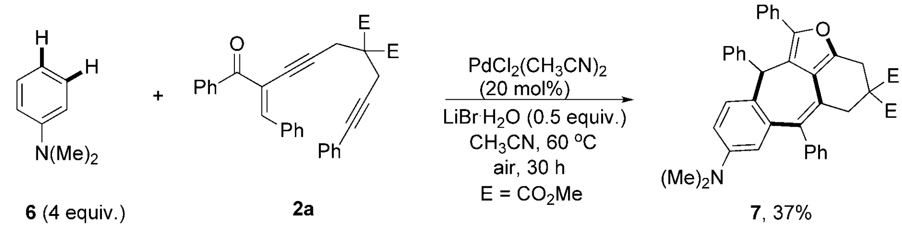
Scheme 3. Plausible mechanism



(2)



(3)



(4)

fused rings using air as oxidant. Further studies encompassing the mechanism, scope and the new reaction design based on diyne-enones are underway in this laboratory and will be reported in due course.

Experimental Section

Typical Procedure for the Synthesis of 3aa (Table 1, entry 1)

$PdCl_2(CH_3CN)_2$ (3.9 mg, 0.015 mmol) was added to a mixture of **1a** (73.5 mg, 0.15 mmol), **2a** (39.3 mg, 0.3 mmol) in CH_3CN (1.5 mL) at 40 °C. After stirring for 18 h, **1a** was consumed completely according to TLC analysis, and then the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexanes:CH_2Cl_2:Et_2O = 4:2:0.1) to give the desired product **3aa** as a white solid; yield: 76 mg (82%); mp 142–145 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.77–7.80$ (m, 1H), 7.64–7.68 (m, 2H), 7.40–7.46 (m, 2H), 7.09–7.33 (m, 14H), 6.03 (s, 1H), 3.78 (s, 3H), 3.76 (d, 1H, $J = 17.4$ Hz), 3.75 (d, 1H, $J = 14.4$ Hz), 3.74 (s, 3H), 3.29 (d, 1H, $J = 17.4$ Hz), 2.97 (s, 3H), 2.64 (d, 1H, $J = 14.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.08$, 170.52, 149.97, 147.83, 143.76, 139.90, 137.94, 136.67, 131.01, 130.04, 128.78, 128.10, 127.43, 126.99, 126.80, 126.75, 126.04, 123.97, 122.18, 121.31, 119.56, 118.57, 117.57, 109.11, 55.82, 53.15, 52.96, 35.94, 33.86, 32.29, 30.11; MS (70 eV): m/z (%) = 619 (52.36) [M^+], 542 (100); HR-MS: m/z = 619.2359, calcd. for $C_{41}H_{33}NO_5$ $(M)^+$: 619.2359.

Supporting Information

Experimental details and copies of $^1H/^{13}C$ NMR spectra of all new compounds are available as supporting information.

Acknowledgements

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[9] Please see the details in Supporting Information.

[10] CCDC 764221 (**3ab**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge form The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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