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# A Fast Track to Indoles and Annulated Indoles through *ortho*- vs *ipso*-Amination of Aryl Halides

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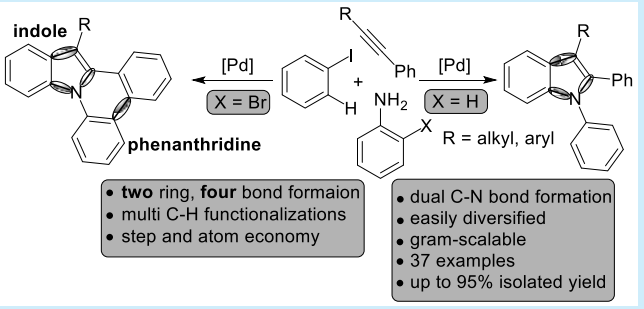
Supporting Information

**ABSTRACT:** A complementary site selective *ortho*- vs *ipso*-amination of aryl halides using non-electrophilic amine sources for construction of indole scaffolds is reported. A palladium-catalyzed alkyne insertion/C−H activation/palladacycle amination via merger of three easily diversified components including iodoarenes, alkynes, and amines delivers indoles with different substitution patterns even in gram scales. By employing *ortho*-bromoanilines, a consecutive annulative $\pi$-extension of indoles proceeds to construct indolo[1,2-*f*]phenanthridine scaffolds via four C−C and C−N bond formations in one pot.

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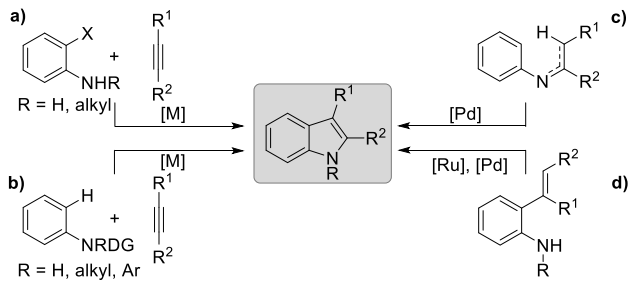
The indole scaffold, one of the most important class of heterocycles, is ubiquitous in a wide variety of organisms and biologically active structures.[1] Many drugs currently on the market contain an indole core nucleus.[2] Some indole ring-containing drug molecules include *Vincristine*, *Reserpine*, *Indomethacine*, *Amedaline*, *Delavirdine*, etc.[3] Despite more than 10 decades of numerous efforts and various strategies developed, organic chemists continue to search for more straightforward and economical ways to construct the pyrrole side of these privillaged structural motifs.[4]

Since Larock's first report on indole synthesis in 1991,[5] transition-metal-catalyzed cyclization of *o*-haloanilines and alkynes has emerged as the most widely adopted protocols toward 2,3-disubstituted indoles and is widely used (Scheme 1a, X = I, Cl, Br, $N_2$).[6] However, the requisite for untrival prehalogention or alkynylation of aniline coupling partners and the use of strong bases restricted the practicality of these reactions. To fulfill the prerequisite in terms of a more sustainable and economical strategy, the oxidative annulation of anilines with alkynes via an ortho C−H functionalization received substantial attention (Scheme 1a, X = H).[7] However, the direct approach from readily available anilines by C−H activation remained a challenging task. Afterward, the directed transition-metal-catalyzed C−H bond functionalization strategy pioneered by Fagnou appeared as an attractive strategy in cyclization reactions for broader substrate scope and higher atom economy (Scheme 1b).[8] These processes are associated with some limitations including the requisite for preinstallment of directing groups (DG) and their removal after construction of indole. Some complementary reports also included preinstallment of olefinic parts on the nitrogen[9] or arene sides[10] of the anilines (Scheme 1c and 1d, respectively).

**Scheme 1. Transition-Metal-Catalyzed Annulation of Anilines**




Despite significant achievements, in all the preparative methods offered, the benzoic ring of indoles is built up of the aryl section of anilines thus comprising limited scope and applications. Building on these pioneering works, new synthetic approaches based on the assembly of indole nucleus directly from more easily diversified building blocks may find great interest and applications and open a new avenue for designing more efficient processes through indole ring constructions.[11]

In situ generated C,C-palladacycles generally prepared from aryl halides are relevant intermediates in Pd-catalyzed reactions utilized to develop *ortho*-functionalizations and new transformations.[12,13] In this regard several alkylations and arylations of palladacycles have been fulfilled. However, amination of C,C-palladacycles is rarely considered and mainly limited to electrophilic nitrogen sources.[14] Recently, Zhang et al. developed an amination reaction of C,C-palladacycles derived

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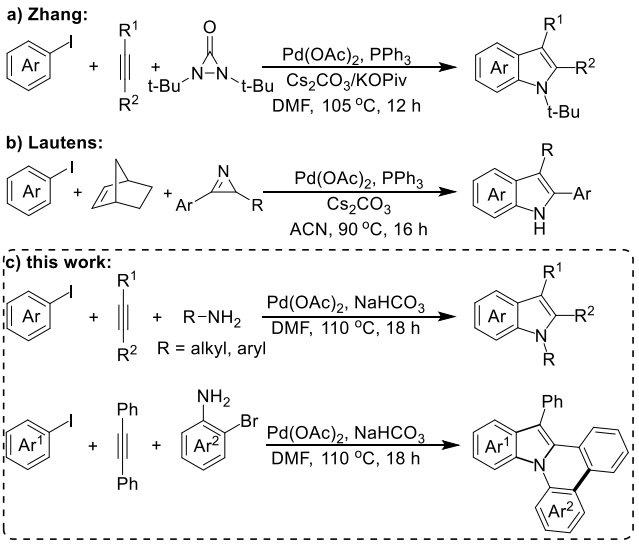
from iodoarenes and alkynes employing di-*tert*-butyldiaziridinone to construct indoles (Scheme 2a).[15] Despite the significance of this contribution the scope of indoles obtained by this course was limited to *N*-*tert*-butylindoles. Lautens group also have described an intermolecular amination of arene norbornene palladacycles with highly strained 2*H*-azirines to build the pyrrole side of indoles (Scheme 2b).[16]

**Scheme 2. Amine Sources for Amination of C,C-Palladacycles in Construction of 2,3-Difunctionalized Indoles**

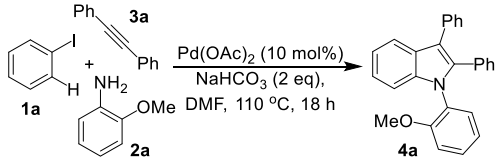



Inspired by these pioneering works and following our interest in palladacycles,[17] we envisioned that synthesis of 2,3-disubstituted *N*-aryl(alkyl)indoles might be accessed through a cascade three-component cycloaddition of haloarenes, alkynes, and more simple and accessible nitrogen sources such as anilines and amines. However, realizing such a cascade owing to various competing reactions may be highly challenging. First, a highly reactive alkyne is supposed to directly react with iodoarene to construct various carbocycles such as fluorenes,[18] phenanthrenes,[19] and naphthalenes.[20] Second, anilines and alkynes are supposed to provide free NH-indoles via classical Larock reaction.[5] Last, an ipso-amination of iodoarene via Buchwald−Hartwig reaction may be an important competing reaction.[21]

Herein, we describe the realization of a palladium-catalyzed annulation cascade that allows the facile synthesis of a variety of valuable 1,2,3-highly functionalized indoles, incorporating three easily diversified building blocks: haloarenes, alkynes, and anilines. Setting the potentially competitive *ipso*-amination as well as benzannulation of iodoarene with an alkyne is key to the success of this domino reaction. Furthermore, by employing *ortho*-bromo anilines as the amine coupling partner, an extra intramolecular arylation leads to two new rings and four C−C and C−N bond formations for construction of indolo[1,2-*f*]phenanthridine scaffolds in one pot.

To realize the palladium-catalyzed arene/alkyne/amine cyclization cascade, iodobenzene **1a**, 2-methoxy aniline **2a**, and diphenyl acetylene **3a** were initially combined under various reaction conditions. After vigorous optimization, we were grateful to find that the cascade indeed did proceed in the presence of a palladium catalyst to afford 1,2,3-triarylindole **4a**. Under the standard conditions employing $Pd(OAc)_2$ (10 mol %) and $NaHCO_3$ (2 equiv) in DMF at 110 °C, the desired indole **4a** was obtained in a promising 90% yield (Table 1, entry 1). The reaction was totally suppressed when the palladium catalyst was removed (entry 2). Screening reaction conditions with respect to palladium salts revealed $Pd(OAc)_2$ to be the most optimal (entries 3−4). While $NaHCO_3$ provided higher yields than other bases such as $K_2CO_3$, $Cs_2CO_3$, KOAc, and $K_3PO_4$, its removal significantly decreased the cyclization yield (entries 5−9, for more details see Supporting Information). Compared to DMF, although DMSO gave a comparable result, other solvents including chlorobenzene, ACN, THF, etc. were undesirable (entries 10−13).

**Table 1. Optimization of Reaction Conditions**[a]




| entry | change from standard conditions | yield[b] |
|---|---|---|
| **1** | **standard conditions** | **90** |
| 2 | no Pd catalyst | 0 |
| 3 | $PdCl_2$ instead of $Pd(OAc)_2$ | 44 |
| 4 | $Pd(dba)_2$ instead of $Pd(OAc)_2$ | 48 |
| 5 | no $NaHCO_3$ | 25 |
| 6 | $K_2CO_3$ instead of $NaHCO_3$ | 78 |
| 7 | $Cs_2CO_3$ instead of $NaHCO_3$ | 71 |
| 8 | KOAc instead of $NaHCO_3$ | 66 |
| 9 | $K_3PO_4$ instead of $NaHCO_3$ | 69 |
| 10 | DMSO instead of DMF | 76 |
| 11 | chlorobenzene instead of DMF | 21 |
| 12 | ACN instead of DMF | 29 |
| 13 | THF instead of DMF | trace |

[a]Reaction conditions: Aryl halide (0.1 mmol), acetylene (1 equiv), amine (2 equiv), Pd catalyst (10 mol %), base (2 equiv), solvent (1 mL), 110 °C, 18 h. [b]Isolated yields.

With optimized conditions in hand, we examined the generality and substrate scope of the palladium-catalyzed three-component coupling cascade for synthesis of multifunctionalized indoles. Ortho-substituted anilines containing alkyl and alkoxy groups exhibited high to excellent reactivity to produce indoles **4a−c** in 75−90% yields (Scheme 3, entries 1−3). Likewise, para-substituted anilines containing alkoxy and susceptible bromo and chloro groups provided the desired products **4d−f** and **4i** in 76−89% yields where the halo groups were preserved in the course of the reaction providing a synthetically useful handle for further functionalizations (entries 4−6 and 9). The method worked well for anilines bearing electron-withdrawing groups as well, and the desired products were obtained albeit in lower yields (entries 7 and 11). Electron-neutral aniline also participated well in this reaction to afford 1,2,3-triphenyl indole **4h** in 83% yield (entry 8). Turning our attention to the scope of iodoarene coupling partner, we realized that the procedure tolerates a range of substitution patterns and functional groups on this substrate. Various electron-rich and deficient iodoarenes exhibited good reactivity under the optimized reaction conditions to afford the desired products in good to high yields (entries 12−18). The reaction was also amenable to naphthalene amines resulting in



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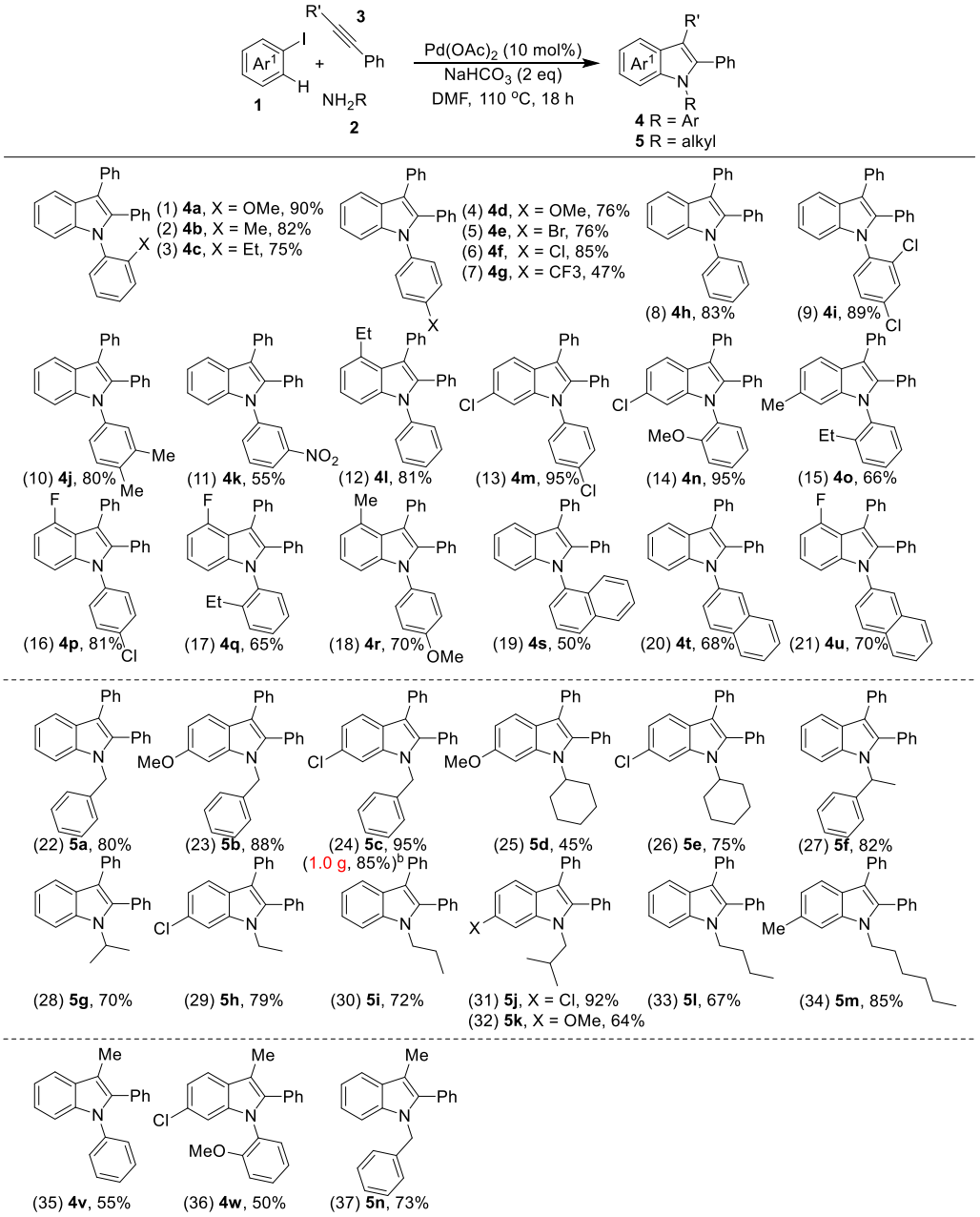
**Scheme 3. Reaction Scope for Construction of *N*-Aryl and *N*-Alkylindoles**[a]




[a]Reactions performed on a 0.1 mmol scale with iodoarene (1 equiv), alkyne (1 equiv), amine (2 equiv), $Pd(OAc)_2$ (10 mol %), DMF (1 mL), 110 °C, 18 h. [b]3.0 mmol of **1** were used.

sterically crowded indoles **4s**–**u** in moderate to good yields, which had not been previously possible in any other way (entries 19–21).

By employing benzylamines instead of anilines, even superior results were obtained so that the desired targets were provided in up to 95% yield (entries 22–24). Motivated by these results, we sought to apply this strategy to the simple production of *N*-alkyl 2,3-diarylindoles. The results showed that three-component cyclization reaction of iodoarenes, diphenylacetylene, and aliphatic amines proceeded smoothly in the same manner to furnish the anticipated *N*-alkyl indoles in 45–92% yields under the optimized reaction conditions (entries 25–34). Notably, a yield of 85% was still obtained when the reaction was scaled up to 3.0 mmol (entry 24).

Intriguingly, when we tried to expand the alkyne scope to aryl alkyl-disubstituted alkynes, assembly of unsymmetrically 2,3-disubstituted indoles with an absolute regioselectivity was realized under standard reaction conditions (entries 35–37, yields 50–73%). The observed high regioselectivity is attributed to a carbopalladation sequence of the internal alkyne in which the relatively large phenyl group of the arylpalladium species approach the internal alkyne from the less hindered end of the internal alkyne due to steric hindrance and replaces the more bulkier group at the 2-position.[22]

To our satisfaction, when 2-bromoaniline as the aminating agent was employed in this multicomponent cyclization process, a fascinating successive cyclization via an intramolecular palladium-catalyzed direct arylation tracked carbo-



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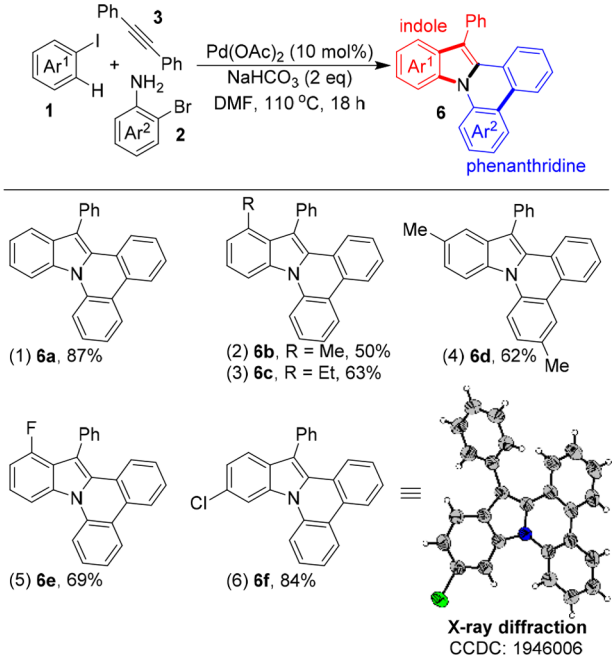
palladation/amination cascade to afford the promising indolophenanthridine scaffold **6a** practically in a single synthetic sequence in 87% isolated yield (Scheme 4, entry

**Scheme 4. Scope of Cascade Construction of Indolophenanthridines**[a]

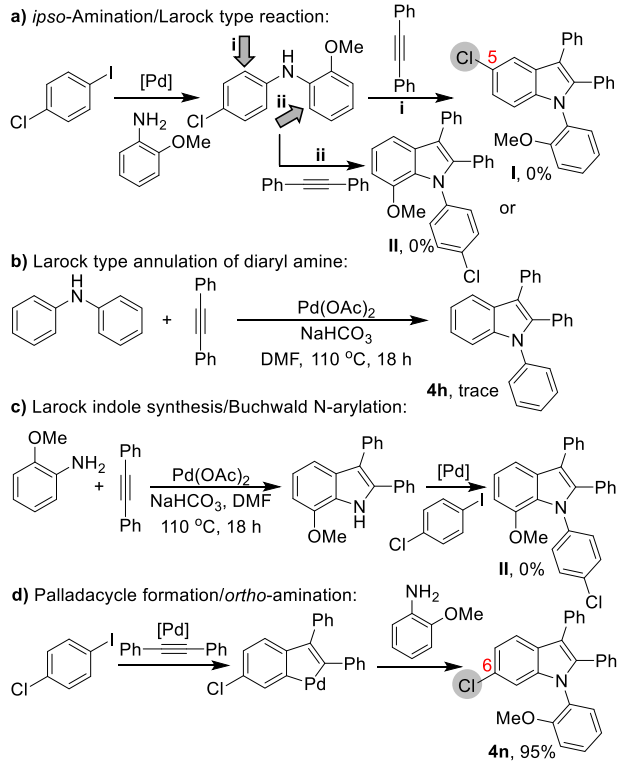



[a]Reactions performed on a 0.1 mmol scale with iodoarene (1 equiv), alkyne (1 equiv), 2-bromoaniline (2 equiv), $Pd(OAc)_2$ (10 mol %), DMF (1 mL), 110 °C, 18 h.

1). This process involves four $Csp^2-Csp^2$ and $Csp^2-N$ bond formations in one process and involves an unprecedented feasible construction of the polycyclic fused indoles directly from readily accessible starting materials. To test the feasibility and scope of the domino cyclization, some *o*-, *m*-, and *p*-substituted iodoarenes were coupled with diphenylacetylene and bromoanilines, where the desired products were obtained in moderate to high yields (entries 2–6, yields 50–84%). The structure of **6f** was unambiguously confirmed by single-crystal X-ray diffraction (CCDC 1946006).

To gain insight into the reaction mechanism and differentiate between three parallel plausible paths, some control experiments using 4-chloroiodobenzene, diphenyl acetylene, and 2-methoxy aniline were carried out (Scheme 5). A plausible early *ipso*-amination via Buchwald–Hartwig reaction trailed with the annulation reaction would result in two possible isomers (Scheme 5a, **I** and **II**), which none were detected in the reaction course. Furthermore, when a diphenylamine was subjected to the standard conditions, only traces of the desired indole **4h** was collected (Scheme 5b). Furthermore, a domino Larock indole synthesis/Buchwald N-arylation of the in situ generated indole may not be the choice, as the substitution pattern of the indole achieved would be quite different (Scheme 5c). These results suggest that a palladacycle is a more likely intermediate in the course of indole construction. A proposed primary palladacycle development followed by amination would render 6-chloro substituted indole **4n** as obtained in this process in 95% isolated yield (Scheme 5d).

**Scheme 5. Control Experiments Used to Elucidate the Reaction Mechanism**




On the basis of the above mechanistic study and literature precedents, a plausible mechanism for the first annulation reaction via amination of the palladacycle **C** is proposed in Scheme 6. The oxidative addition of iodoarene to palladium(0) results in the aryl palladium species **A** which, on carbopalladation reaction with alkyne,[23] forms styryl palladium species **B**. Subsequent intramolecular C–H activation via a five-membered palladacycle[19e] gives palladacycle **C**. Next, an uncommon trapping of the palladacycle with aryl(alkyl)amines occurs to develop *ortho*-amination of iodoarene. Formation of palladium-amine complex **E** and subsequent reductive elimination finish the intriguing dual amination of an arene and alkyne to construct the pyrrole side of the indole.

Furthermore, by employing an *ortho*-bromoaniline coupling partner, the annulation reaction proceeds even in a more unusual manner. Although all previous reports have evidenced an oxidative addition of the chelating *ortho*-haloanilines to Pd(II) species for construction of a Pd(IV) complex,[24] however, our observation demonstrates an unprecedented direct amination of the palladacycle with *ortho*-bromoanilines in contrast (Scheme 6b, **G** vs **F**). An ultimate reductive elimination leads to the indolophenanthridine **6** adduct and regeneration of palladium(0).[25]

In conclusion we have uncovered a palladium-catalyzed annulation cascade for construction of highly substituted indoles from merger of three easily diversified components. This method represents the first example of forming C–N bonds at the *ortho*-carbon via amination of C,C-palladacycles with nonelectrophilic nitrogen sources. Accordingly, this controllable domino reaction enables a rapid access to a diverse range of indoles including several previously unsynthesized scaffolds mostly in high to excellent yields. In addition, the cascade cyclization of the same substrates employing *o*-



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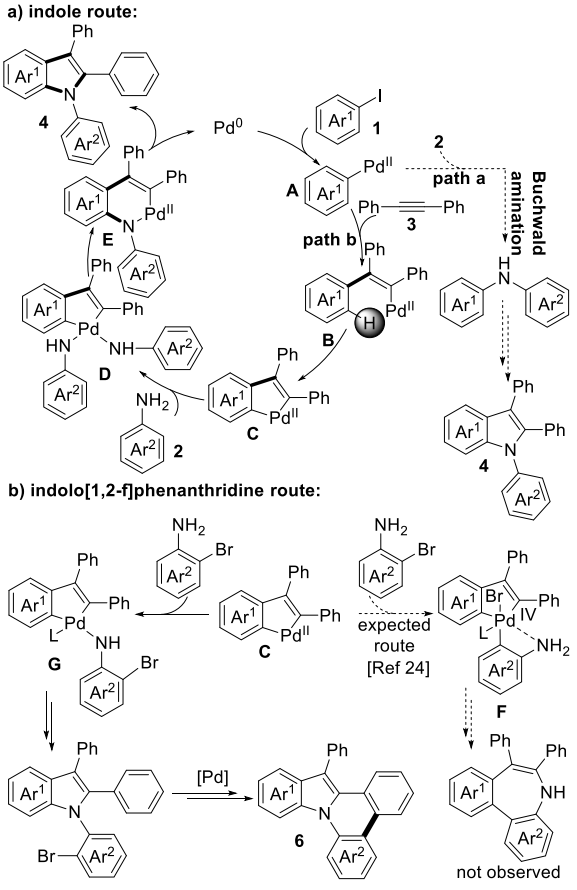
**Scheme 6. Plausible Mechanism Accounting for Domino Annulation Reactions**




haloanilines leads to an unusual construction of indolo[1,2-*f*]phenanthridine frameworks in competitive pathways. Our novel method for construction of indoles bearing flexible substituents at each point of the indole ring complements the classic routes to highly substituted indoles. The method is scalable and mild and obviates any requisite for directing groups or oxidants. Detailed mechanistic studies to realize the dual C−N bond formation steps are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04202.

Experimental procedures and compound characterization data, including the $^{1}H/^{13}C$ NMR spectra (PDF)

### Accession Codes

CCDC 1946006 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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