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$Csp^2–Csp^2$ and $Csp^2–N$ Bond Formation in a One-Pot Reaction between *N*-Tosylhydrazones and Bromonitrobenzenes: An Unexpected Cyclization to Substituted Indole Derivatives

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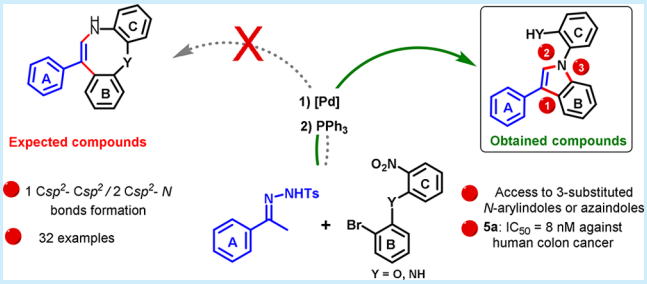
Supporting Information

ABSTRACT: A novel, sequential, palladium-catalyzed, cross-coupling reaction using *N*-tosylhydrazone and bromonitrobenzene derivatives followed by reductive cyclization has been developed. This transformation providing an efficient route to unexpected *N*-arylindole derivatives involves, in a one-pot reaction, the formation of one $Csp^2–Csp^2$ bond and two $Csp^2–N$ bonds together with the cleavage of one $Csp^2–$heteroatom bond. Evaluation of the biological activity led to the identification of compound **5a**, which displays potent activity at nanomolar concentrations against human colon carcinoma cell line.



N-Tosylhydrazones have captured great interest among scientists in the past decade as versatile coupling partners in both transition-metal-catalyzed and metal-free cross-coupling reactions for the construction of carbon−carbon and carbon−heteroatom bonds.[1] Therefore, *N*-tosylhydrazones are used as versatile synthons in the synthesis of a wide range of heterocyclic compounds. Our involvement in the chemistry of 1,1-diarylethylene derivatives, combined with our endeavor to develop novel isocombretastatin A-4 analogues[2] as interesting antitumor compounds, led us to explore a series of Pd- or Cu-catalyzed cross-coupling reactions of *N*-tosylhydrazones with various partners to generate a library of potentially active compounds.[3] On the other hand, nitrogen heterocycles are common fragments of a large number of FDA-approved drugs and in medicinal chemistry.[4] Some of them are routinely used as potential bioisosteres for a variety of functional groups in drug optimization processes.[5] Recently, we developed a one-pot two-step reaction of *N*-tosylhydrazones and *ortho*-nitrobenzenes for the synthesis of variously substituted 3-arylindole and 2,3-diarylindole derivatives (Figure 1, eq 1).[6] The process involves the formation of an olefin intermediate A, obtained through palladium-catalyzed carbene coupling reaction followed by reductive cyclization pursuing a Cadogan mechanism in the presence of PPh_3. This method was also successfully applied to the synthesis of (1-arylvinyl)carbazoles by reaction between hydrazones and bromonitrobiphenyl substrates. Due to the generality of the method, we aimed to apply it to synthesize new building blocks while showing their efficacy in the context of our medicinal chemistry program. Consequently, we attempted at first to prepare new isoCA-4 analogues bearing eight-membered ring heterocycles by coupling the *N*-tosylhydrazone **1** with the corresponding electrophilic coupling partners **2**, then mediating the reductive cyclization in the presence of PPh_3 (Figure 1, eq 2).

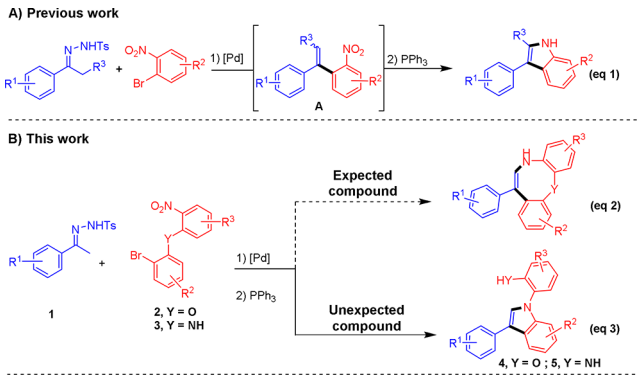


Figure 1. Palladium-catalyzed one-pot reaction of *N*-tosylhydrazones and 2-nitrobromoarenes.

Initially, *N*-tosylhydrazone **1a**, derived from (3,4,5-trimethoxy)acetophenone, was treated with 1-bromo-2-(2-nitrophenoxy)benzene **2a** in the presence of $Pd_2(dba)_3$·

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Org. Lett. XXXX, XXX, XXX−XXX

$CHCl_3$/XPhos as the catalytic system and LiO*t*Bu as the base in dioxane (Figure 2). When the first coupling reaction is

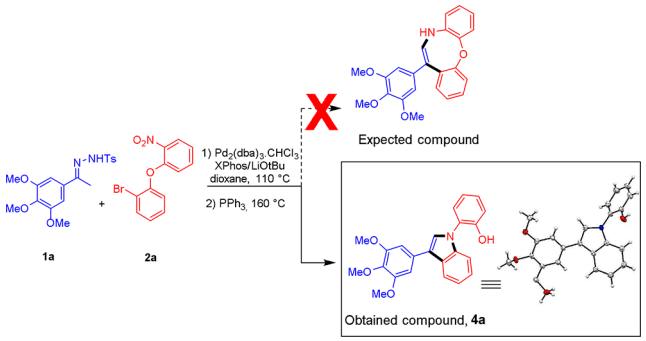


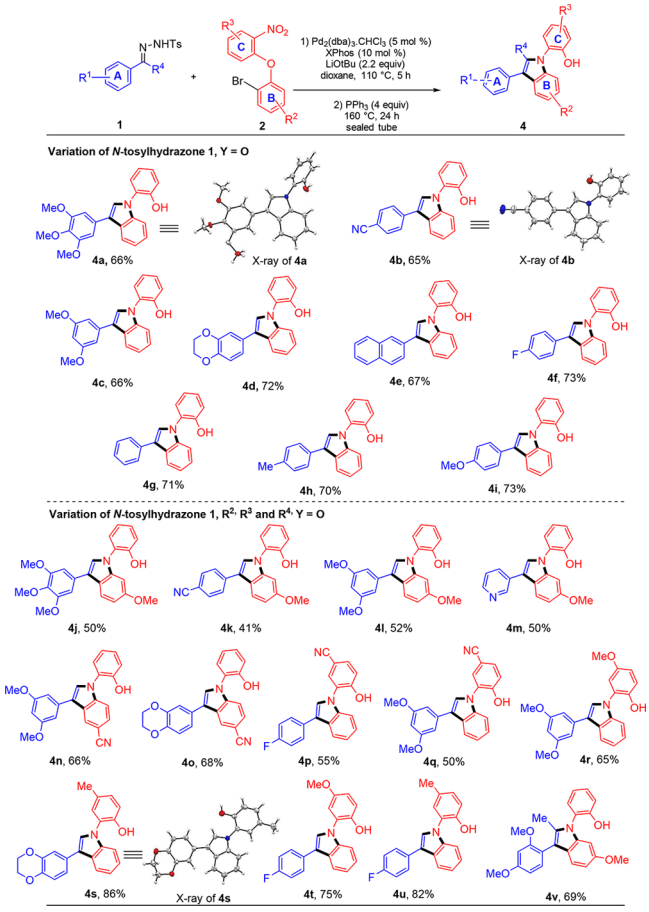
Figure 2. Unexpected formation of *N*-arylindole from *N*-tosylhydrazone and bromo(nitrophenoxy)benzene.

completed (monitoring by HPLC), the reductive cyclization was realized in a one-pot sequence by the addition of PPh_3 (Figure 2). Under these conditions, the eight-membered ring heterocycle was not detected at all. We have discovered that the reaction gives rise to an unexpected cyclization product **4a**, resulting from a sequence involving one Csp^2–Csp^2 and two Csp^2–N bond formations, together with a Csp^2–O bond cleavage. This new cyclization process appears to involve a mechanistically fascinating nitrene rearrangement and rearomatization. The structure of this new *N*-arylindole **4a** was confirmed by NMR and X-ray analysis. These results were also very promising and interesting as the indole moiety is one of the most prevalent heterocycles in nature,[7] and one-pot strategies for the synthesis of indole derivatives have been a unique field of study.[8] In particular, *N*-arylindoles are displayed in a various number of biologically and pharmaceutically significant compounds.[9] Hence, incorporating these *N*-arylindoles within the structure of isoCA-4 can result in a novel series of interesting compounds.

We then studied the scope of the reaction with respect to the *N*-tosylhydrazones **1** and 2-bromo-2′-nitrodiphenyl ethers **2** or 2-bromo-*N*-(2-nitrophenyl)anilines **3** partners (Scheme 1). It should be noted that compounds **2** and **3** were easily synthesized by an aromatic nucleophilic substitution between *ortho*-nitrohaloarenes and 2-bromophenol with the ability of diverse substitution on both aryl units (see Supporting Information (SI)). The reaction appears to be insensitive to electronic properties of the *N*-tosylhydrazone partners: both electron-rich (e.g., **4a** and **4h**) and electron-deficient (e.g., **4b** and **4f**) undergo effective coupling in similarly good yields. Functional groups such as nitrile (**4b**, **4k**) and fluorine (**4f**, **4p**) are conserved in the reactions. Hydrazones bearing heterocycles are also competent coupling partners (cf. **4d**, **4m**, **4o**, **4s**). Next, we explored modifications on the electrophilic partners **2** and **3**. The coupling of building blocks containing different substituents (R^2, R^3, and R^4) using the novel reaction developed in this study yielded products having skeletal complexity and diversity (cf. **4j**–**v**).

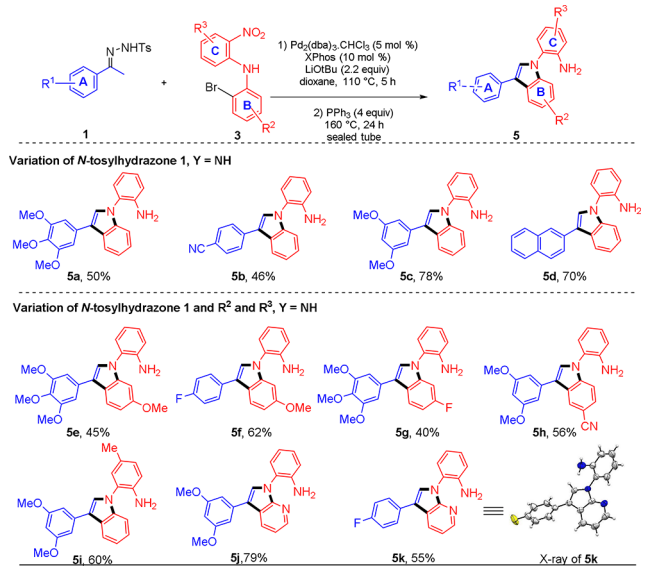
Again, 2-bromo-2′-nitrodiphenyl ethers **2** having electron-withdrawing or electron-donating groups on both aromatic rings B and C were also tolerated. Structures of **4b** and **4s** were characterized by X-ray analyses. Encouraged by the results above, we envisioned widening the generality of this method to substrates **3** having a nitrogen atom as the linker between rings B and C. As expected, coupling with different *N*-tosylhydrazones afforded the desired indole derivatives **5** in good yields

Scheme 1. Pd-Catalyzed One-Pot Synthesis of *N*-Phenylindolylphenols



(compounds **5a**–**k**, Scheme 2). To further explore the flexibility of this cascade reaction, we attempted to react heterocyclic electrophilic partners with *N*-tosylhydrazones. The coupling of 3-bromo-*N*-(3-nitrophenyl)pyridin-2-amine with the corresponding *N*-tosylhydrazones was very applicable, giving rise to

Scheme 2. Pd-Catalyzed One-Pot Synthesis of *N*-Phenylindolylanilines



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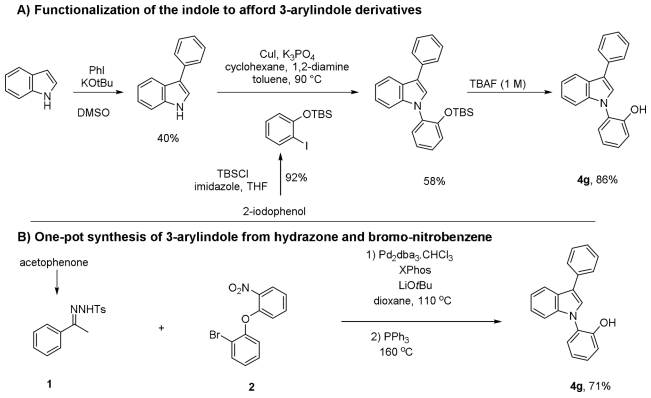
new azaindole derivatives (compounds **5j**–**k**). X-ray analysis of **5k** showed that the same mechanism is followed while changing the linker (O to NH).

To get a comparative study between this method and currently available process, we synthesized compound **4g** starting from commercially available 3-iodophenol and indole (Scheme 3A).

Scheme 3. Comparative Study for the Synthesis of 3-Arylindole 4g

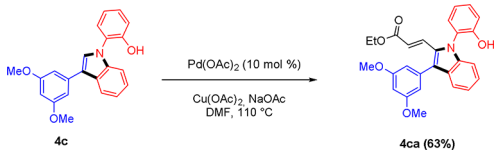


First, 3-phenyl-1*H*-indole was obtained in a 40% yield after a metal-free C3-arylation of the indole.[10] Then, a copper-catalyzed coupling with the protected phenol was conducted, leading to the arylindole in a 58% yield.[11] The latter underwent a deprotection step to afford **4g** in an 86% yield. According to this three-step strategy, **4g** was obtained in a 20% overall yield.

On the other hand, using our method (Scheme 3B), hydrazone **1** was obtained in a nearly quantitative yield (98%) starting from acetophenone. Then, coupling was realized using our standard conditions, thus leading to **4g** in a 70% overall yield. This clearly shows the advantage of this new method in terms of the number of steps and the overall yield.

Finally, to obtain more molecular diversity on our scaffold, we studied the oxidative C2 olefination of indoles via Pd-catalyzed C–H bond activation. The reaction of **4c** with ethyl acrylate in the presence of the $Pd(OAc)_2/Cu(OAc)_2$ catalyst system[12] (Scheme 4) proceeded efficiently even in the presence of the hindered 3,5-dimethoxyphenyl group at C3-position, affording the desired compound **4ca** in a 63% yield.

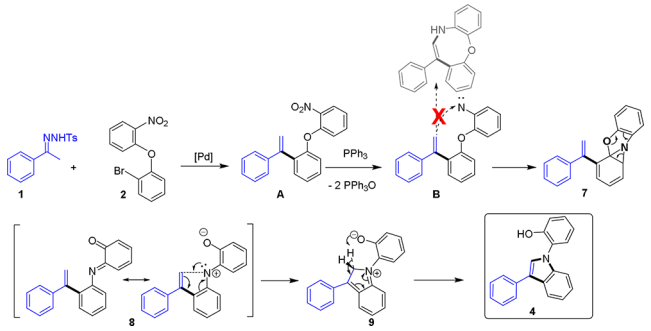
Scheme 4. Pd-Catalyzed C–H Olefination of Indoles



To clarify the cascade reaction mechanism, the coupling intermediate A (Scheme 5) was first isolated and identified, and then the cyclization was conducted in a separate step to confirm that it was mediated with the aid of PPh_3 without the incorporation of any reagent or the catalyst from the coupling step. The mechanism was suggested as it first proceeded by deoxgenation of the nitro group forming the nitrene species B. Since the expected eight-membered ring was not formed, we can rule out the insertion of nitrene into the terminal double bond.

On the other hand, a cyclization of nitrene B could lead to the aziridination of the proximal electron-rich aryl ring 7.[13] The

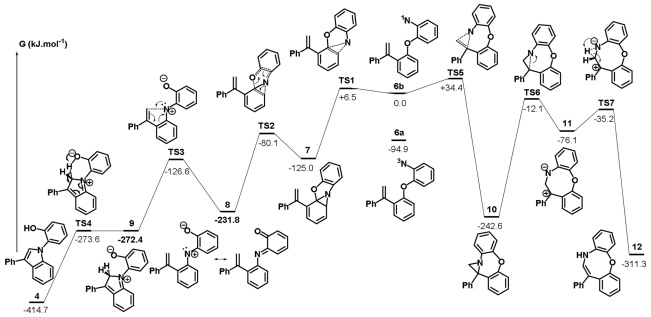
Scheme 5. Proposed Mechanism



highly strained aziridine ring opens to give *o*-iminoquinone **8**, which upon subsequent 6π-electrocyclization delivers the 1,3-diarylindole **4**.

To gain better insight into the reaction mechanism, and to obtain the preference for **4** and **5** over the expected products, we have carried out a computational study at the DFT level (Scheme 6; see the SI for computational details). The nitrene species **B** (**6a**

Scheme 6. DFT Computation of the Mechanism



in its triplet state, **6b** in its singlet state) adds to CC double or aromatic bonds to form **7** and **10**, which include the aziridine moiety, with the former being more easily formed. A rearrangement from **7** followed by an electrocyclization and a proton transfer leads easily to **4**, whereas ring opening from **10** leading to **12** after proton transfer is energetically more difficult. Furthermore, **4** is significantly more stable than **12**, indicating that **4** is both the kinetic and thermodynamic product, in agreement with experiments.

Schematic potential energy surface for the cyclization reactions leading to the expected (**12**) and observed (**4**) compounds from the nitrene species obtained at the IEFPCM(1,4-dioxane)-B3LYP-GD3BJ/6-311++G(2d,2p)//IEFPCM(1,4-dioxane)-B3LYP/6-311G(d,p) level.

After the success of synthesizing these new compounds, their potency was measured in cell viability studies using HCT-116 human colon cancer cells. A fluorimetry-based assay was used for the determination of the drug concentration required to inhibit cell growth by 50% after incubation in the culture medium for 72 h. IsoCA-4 was included as a positive control to validate the quality of the experimental results.

The results are shown in Table 1. None of these 2-(3-aryl-1-indol-1-yl)phenol analogues (**4a**,**b**, **4j**, and **4k**) exhibited significant antiproliferative activity against HCT-116 cells. However, indoles having aniline instead of phenol showed interesting antiproliferative activity. The best activities were obtained with compounds having the trimethoxyphenyl group (cf. **5a** and **5g** vs **5k**). The assay showed that compound **5a** (IC_{50}

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Org. Lett. XXXX, XXX, XXX–XXX

Table 1. Cytotoxic Activity of Selected Derivatives Against HCT-116 Cells[a]

compound	IC_{50} (nM)[b]	compound	IC_{50} (nM)[b]
4a	na[c]	**5a**	8 ± 2.0
4b	na[c]	**5g**	14.7 ± 3.1
4j	na[c]	**5k**	37.2 ± 3.8
4k	na[c]	isoCA-4	2.2 ± 1.2

[a]HCT-116 human colon carcinoma cells. [b]Compound concentration required to decrease cell growth by 50%. [c]Not active.

= 8 nM) greatly inhibits the cell growth of the human colon carcinoma cells,[14] with an excellent antiproliferative activity close to the reference compound isoCA-4. Our finding disclosed a new scaffold, and this compound could be considered as a new lead in the battle against cancer.

In summary, we have developed an efficient one-pot, two-step reaction of *N*-tosylhydrazones and bromonitrobenzene derivatives to afford *N*-phenylindolylphenols and *N*-phenylindolylanilines. This reaction proceeded through the formation of an olefin intermediate via Pd-catalyzed carbene coupling reaction, followed by a PPh_3-promoted reductive cyclization. This transformation was found to involve the formation of one Csp^2-Csp^2 and two Csp^2-N bonds formation, together with a Csp^2-O bond cleavage. Among evaluated derivatives, the new compound **5a** exhibited the highest cytotoxic activity (IC_{50} = 8 nM) against human colon cancer cell lines. Finally, the new scaffold and biological profile of **5a**, along with the established synthetic protocol, provide a collectively attractive approach that may shed light onto the path toward the discovery of new and potent antitumor agents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03422.

Experimental procedures, characterization data, X-ray analysis and computational methods, ^1H NMR and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1576649−1576652 contain 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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