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# Pd(II)-Catalyzed One-Step Construction of Cycloalkane-Fused Indoles and Its Application in Formal Synthesis of (±)-Aspidospermidine

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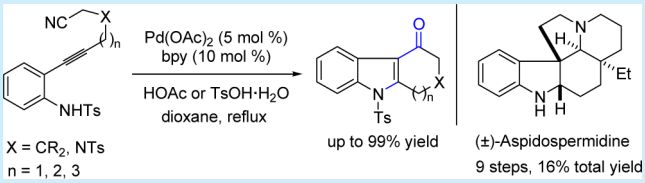
Supporting Information

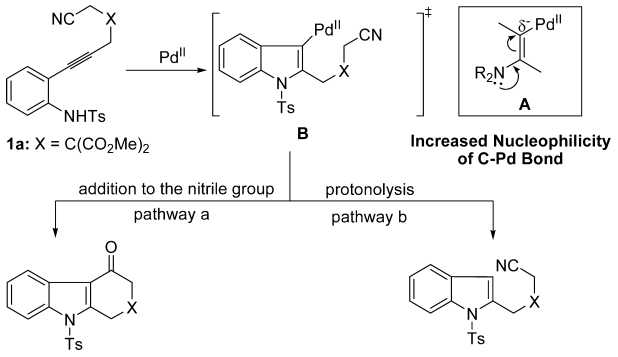
**ABSTRACT:** A highly efficient, redox-free Pd(II)-catalyzed tandem cyclization reaction initiated by intramolecular aminopalladation of alkynes followed by nucleophilic addition to nitriles is developed. This method provides a versatile approach for the synthesis of six- to eight-membered ring-fused indoles in one step and has also shown advantages in the formal synthesis of (±)-aspidospermidine.




Cyclohexa[*b*]indoles, as well as cyclopenta-, cyclohepta-, and cycloocta[*b*]indoles, are found to be core structures in a broad category of natural products and synthetic pharmaceuticals.[1] To date, much work has been directed toward the installation of five- to eight-membered rings onto indoles. The most commonly used method is the Fischer indole synthesis which, although very powerful, still holds some drawbacks such as harsh reaction conditions and the use of various kinds of highly functionalized hydrazines and cyclo-ketones which are not very easily accessed.[2] Recently, although many novel methods for the synthesis of cycloalkane-fused indoles have been reported,[3] methods to install the above ring systems onto indoles in a single step are still rare.[4] In addition, if a functional group such as a carbonyl group can be introduced in the fused indoles, considerable conveniences may be achieved in the further transformations.

In recent years, transition-metal-catalyzed nucleophilic addition reactions to nitriles have been developed as efficient approaches for the synthesis of aryl ketones and other useful compounds.[5−7] These reactions exhibit many advantages compared to the classical Grignard reaction. They are normally catalytic, atom-economic, easily handled, and tolerant of many functional groups. Generally, the nitrile group is less reactive than other carbon−heteroatom multiple bonds such as carbonyl group or imines in palladium chemistry. However, from our previous work, it was found that the vinylpalladium species can add to nitriles easily in some acetoxypalladation-initiated reactions due to the increased polarity of the C−Pd bond caused by the electron-donating effect of the oxygen atom at the α-position.[8] On the basis of this work, we wondered if the electron-donating effect of the nitrogen atom at the α-position (Scheme 1, species **A**) could also increase the polarity of the C−Pd bond, which may promote the nucleophilic addition to the nitriles. As far as we know, such tandem reactions initiated by an aminopalladation of an alkyne and an addition to the nitriles as the quenching step of the carbon−palladium bond have not been reported.

**Scheme 1. Aminopalladation-Initiated Nucleophilic Addition to Nitriles**




With these considerations in mind, we initiated our explorations by using **1a** as the model substrate. It was proposed that a Pd(II) intermediate **B** can be easily formed through *trans*-aminopalladation of substrate **1a** in Scheme 1,[9] and the subsequent addition of the C−Pd bond to the nitrile group led to the expected cyclohexa[*b*]indole (Scheme 1, pathway a). According to the literature, the C−Pd bond in species **B** is not stable: it undergoes protonolysis very easily, especially when the reaction counterpart is an inert nitrile group (Scheme 1, pathway b).[10] We may enable the expected pathway in two ways: one strategy is to stabilize the C−Pd bond in species **B** by adding ligands, another way is to activate the nitrile group.

First, we tested several Pd(II) catalysts using 2,2′-bipyridine as the ligand. $Pd(OAc)_2$, $PdCl_2$, and some cationic Pd(II) catalysts showed no reactivity under the neutral conditions (Table 1, entries 1−6), while under the basic conditions, cyclization product **2a** cannot be detected, and only protonolysis product **3** was formed even when no catalyst

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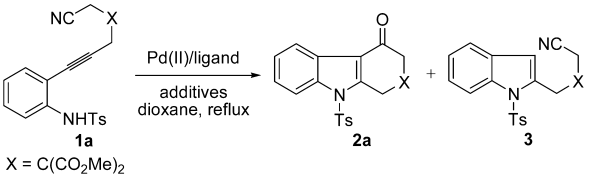
**Table 1. Optimization of the Reaction Conditions**[a]



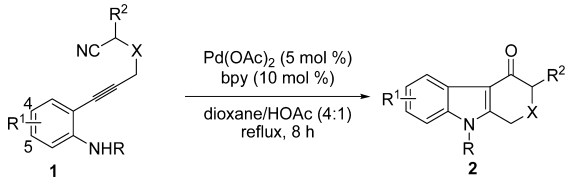

| entry | catalyst | ligand | additives | product (yield, %)[b] |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | bpy | | N.R. |
| 2 | $Pd(TFA)_2$ | bpy | | N.R. |
| 3 | $Pd(CH_3CN)_4(BF_4)_2$ | bpy | | N.R. |
| 4 | $PdCl_2$ | bpy | | N.R. |
| 5[c] | $(bpy)Pd(H_2O)_2(OTf)_2$ | | | N.R. |
| 6 | $[(bpy)Pd(\mu\text{-}OH)]_2(OTf)_2$ | | | N.R. |
| 7 | $Pd(OAc)_2$ | | LiBr | **3** (trace) |
| 8 | $Pd(OAc)_2$ | bpy | $Cs_2CO_3$ | **3** |
| 9[d] | | bpy | $Cs_2CO_3$ | **3** |
| 10[e] | $Pd(OAc)_2$ | bpy | HOAc | **2a** (99) |
| 11 | $Pd(OAc)_2$ | bpy | $TsOH{\cdot}H_2O$ | **2a** (92) |
| 12[e] | | bpy | HOAc | N.R. |
| 13[f] | $Pd(OAc)_2$ | dppp | HOAc | N.R. |

[a]The reaction was carried out using **1a** (0.2 mmol), Pd(II) catalyst (5 mol %), ligand (10 mol %), and additives (2 equiv) at reflux for 8 h in dioxane (2.0 mL). [b]Yield of **2a** was isolated yield. The yield of **3** was not determined. [c]MeOH/$H_2O$ (1:1) was used as the solvent. [d]MeCN was used as the solvent. [e]Dioxane/HOAc (4:1) was used as the solvent. [f]The amount of dppp was 1.2 equiv based on palladium acetate.

was added (Table 1, entries 7–9). Finally, to our delight, when the reaction was conducted under acidic conditions, the expected cascade cyclization proceeded very smoothly to give product **2a** in high yield, indicating that the addition of an acid may enhance the reactivity of the nitrile group. With acetic acid as the additive, almost quantitative yield was obtained, while $TsOH{\cdot}H_2O$ also provided 92% yield (Table 1, entries 10 and 11). Dioxane was found to be the best solvent for the reaction. Control tests showed that no reaction occurred in the absence of the catalyst (Table 1, entry 12). Other bidentate ligands such as dppp inhibited the cyclization (Table 1, entry 13).

Having established the optimal conditions, we set out to investigate the substrate scope of this cyclization reaction for the synthesis of cyclohexa[*b*]indoles. First, substrates with electron-withdrawing groups on the nitrogen atom were tested. It was found that the tosyl group was most suitable for the reaction, and the mesyl group gave a slightly lower yield. No cyclization product was formed when the substituent is a Boc (Table 2, entries 1–3). Substrate without substituent on the nitrogen atom was also tried, and no product was detected under the same conditions. Then, the substituents on the benzene ring were investigated. Substrates with electron-donating groups such as methyl or methoxy gave excellent yields, while electron-withdrawing groups such as trifluoromethyl gave a lower yield (Table 2, entries 4–7). Substrate with a fluorine atom on the benzene ring also worked well (Table 2, entry 8). Finally, the synthesis of the heterocyclic ring fused indoles was explored. Substrate **1i** (X = NTs) can be transformed to the product **2i** efficiently. However, substrate **1j** (X = O) only provided a trace of the product (Table 2, entries 9 and 10). Moreover, an $\alpha$-substituted nitrile also gave the excellent yield (Table 2, entry 11).

**Table 2. Construction of Cyclohexa[*b*]indole**[a]

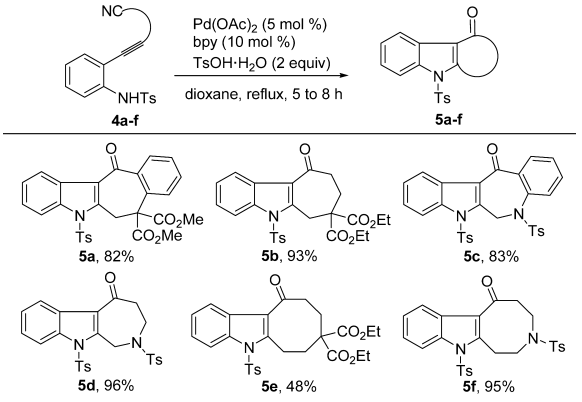



| entry | R | $R^1$ | $R^2$ | X | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Ts | H | H | $C(CO_2Me)_2$ (**1a**) | 99 (**2a**) |
| 2 | Ms | H | H | $C(CO_2Me)_2$ (**1b**) | 94 (**2b**) |
| 3[c] | Boc | H | H | $C(CO_2Me)_2$ (**1c**) | 0 |
| 4 | Ts | 4-Me | H | $C(CO_2Me)_2$ (**1d**) | 95 (**2d**) |
| 5 | Ts | 5-MeO | H | $C(CO_2Me)_2$ (**1e**) | 98 (**2e**) |
| 6 | Ts | 4-Cl | H | $C(CO_2Me)_2$ (**1f**) | 79 (**2f**) |
| 7 | Ts | 4-$CF_3$ | H | $C(CO_2Me)_2$ (**1g**) | 75 (**2g**) |
| 8 | Ts | 4-F | H | $C(CO_2Me)_2$ (**1h**) | 90 (**2h**) |
| 9 | Ts | H | H | NTs (**1i**) | 94 (**2i**) |
| 10 | Ts | H | H | O (**1j**) | trace |
| 11 | Ts | H | Et | $CH_2$ (**1k**) | 96 (**2k**) |

[a]The reaction was carried out using **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), and bpy (10 mol %) at reflux for 8 h in dioxane/HOAc (2.0:0.5). [b]Isolated yield. [c]The starting material was recovered when HOAc was used as the acid, and the reaction became complicated when $TsOH{\cdot}H_2O$ was added.

To expand the scope of this cyclization reaction further, substrate **4a** (Scheme 2) was tried for the synthesis of

**Scheme 2. Construction of Cyclohepta- and Cycloocta[*b*]indoles**[a]




[a]The reaction was carried out using **4a–f** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), bpy (10 mol %), and $TsOH{\cdot}H_2O$ (2 equiv) at reflux for 5–8 h in dioxane.

cyclohepta[*b*]indole. Disappointingly, no expected product was detected under the standard conditions for cyclohexa[*b*]-indoles. It was suggested that intermolecular acetoxypalladation of the alkyne might also occur in the first step in the presence of acetic acid, which made the reaction complicated.[8] We then tried other acids such as $H_3PO_4$ and $TsOH{\cdot}H_2O$. Fortunately, when 2 equiv of $TsOH{\cdot}H_2O$ was added, cyclization product **5a** was obtained in 83% yield. Some other substrates were also examined for the synthesis of cyclohepta[*b*]indoles. Substrates containing a nitrogen atom gave excellent yields (Scheme 2, **5c** and **5d**). Using these optimal conditions, cycloocta[*b*]indoles were also formed successfully (Scheme 2, **5e** and **5f**), which were previously not very easily accomplished. In the literature,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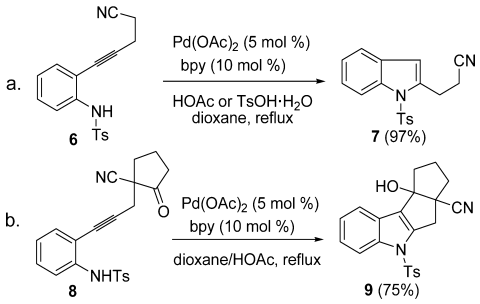
only a few examples were reported on installing eight-membered rings onto indoles but with poor conversion or requiring equivalents of metals.[4d,11]

Having installed six- to eight-membered rings onto indoles successfully, we set out to investigate the construction of cyclopenta[*b*]indoles. The tandem cyclization did not occur at all and only protonolysis product **7** was obtained when substrate **6** was used for the reaction (Scheme 3, eq a).

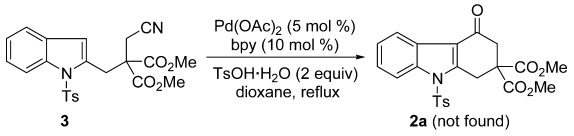
**Scheme 3. Construction of Cyclopenta[*b*]indoles**




Interestingly, when compound **8** was used under the standard conditions for cyclohexa[*b*]indoles, the carbon−palladium bond added to the carbonyl group preferentially to form product **9** in 75% yield (Scheme 3, eq b). These results indicated that carbonyl groups are more reactive than nitrile groups in this reaction.

To gain further insight into the possible mechanism, a control experiment was conducted. Substrate **3** was employed using the same conditions as Scheme 2, but no reaction occurred at all (Scheme 4), indicating that our reaction is a

**Scheme 4. Control Experiment for the Possible Mechanism**

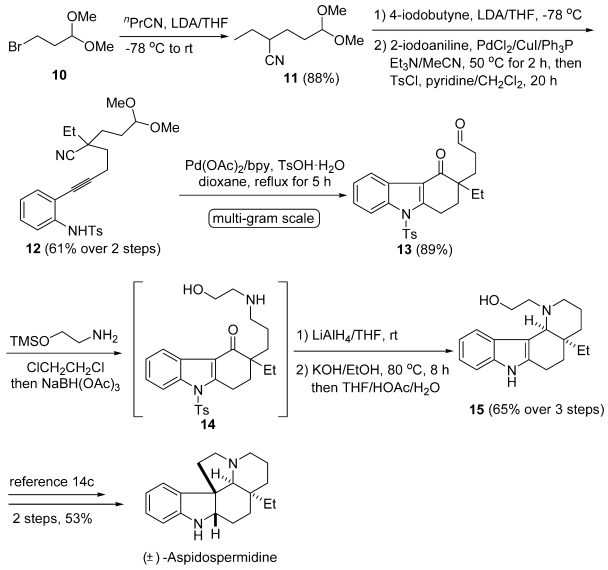



tandem cyclization (as shown in Scheme 1, pathway a), but not a one-pot, two-step process (first formation of **3**, followed by Friedel−Crafts type reaction or palladium catalyzed nucleophilic addition).[12]

Because of the general fact that cyclohexa[*b*]indole cores are privileged heterocyclic ring systems found in a large number of indole alkaloids, we became interested in applications of this method in the synthesis of natural products. (±)-Aspidospermidine was then chosen as the target molecule. As a representative member of the indole alkaloids isolated from aspidosperma,[13] aspidospermidine has attracted many chemists' interests due to its unique fused-ring system. So far there have been dozens of articles about synthetic approaches to racemic and optically active aspidospermidine.[14] We hoped to construct the skeleton of this compound using our method as a key step. The newly formed carbonyl group would undergo further transformations to provide great conveniences in the later processes (Scheme 5).

The synthesis was started with the starting material **10**. Compound **11** was obtained in 88% yield via a nucleophilic substitution with butyronitrile using LDA as the base. Then a similar nucleophilic reaction was performed by reacting **11** with 1-iodo-3-butyne, and the product was used directly for the next

**Scheme 5. Synthetic Routes for (±)-Aspidospermidine**




Sonogashira coupling without purification.[15] The coupling product was treated with *p*-toluenesulfonyl chloride, and compound **12** was obtained in 61% yield over two steps from **11**. Compound **12** was transformed to **13** successfully in 89% yield using the method described in this paper. It was noteworthy that this reaction can be conducted on a multigram scale, and the catalyst amount can be reduced to 1 mol %. Then **13** was transformed to **14** via reductive amination, and **14** was used directly for the next step without purification. The carbonyl group in **14** was reduced to hydroxy group using $LiAlH_4$, after which the Ts group was removed using KOH as the base and EtOH as the solvent under 80 °C. The crude product was worked up with acetic acid and led to amino alcohol **15** in 65% yield over three steps. The transformation of **15** to (±)-aspidospermidine has been reported.[14c]

In conclusion, we have developed a highly efficient method for the construction of six- to eight-membered ring-fused indoles via intramolecular aminopalladation of alkynes followed by nucleophilic addition to nitriles. For cyclohepta[*b*]indoles and cycloocta[*b*]indoles, $TsOH·H_2O$ must be used instead of HOAc to avoid the acetoxypalladation-initiated side reactions. Still unclear is the failure of constructing cyclopenta[*b*]indoles using this method, and study on this subject is ongoing. This reaction was catalyzed by palladium(II) without the necessity of a redox system. The method has shown its application in the formal synthesis of (±)-aspidospermidine and may find further applications in the synthesis of other indole alkaloids.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, compound characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

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### Notes

The authors declare no competing financial interest.


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