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Synthetic Methods

Regio- and Chemoselective N-1 Acylation of Indoles: Pd-Catalyzed Domino Cyclization to Afford 1,2-Fused Tricyclic Indole Scaffolds

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Abstract: A concise method for the synthesis of 1,2-fused tricyclic indole scaffolds by domino cyclization involving a Pd-catalyzed Sonogashira coupling, indole cyclization, regio- and chemoselective N-1 acylation, and 1,4-Michael addition is reported. This method provides straightforward access to tetrahydro[1,4]diazepino[1,2-*a*]indole and hexahydro[1,5]diazocino[1,2-*a*]indole scaffolds.

Fused polycyclic indole scaffolds[1–4] (Figure 1) are found in numerous natural products and synthetic drug molecules. Important examples include streptocarbazoles and evodiagenine (Figure 1), which have a tetrahydro[1,4]diazepino[1,2-*a*]indole core structure. These compounds have attracted the attention

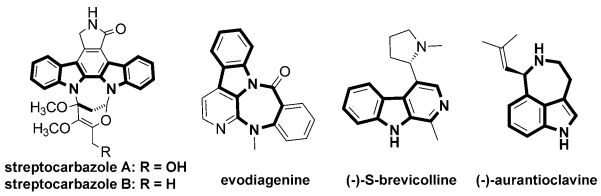
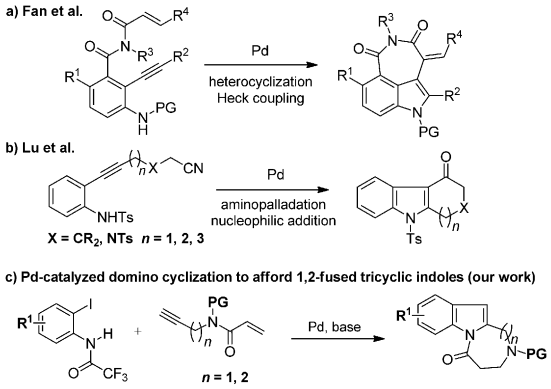


Figure 1. Natural products with fused polycyclic indole scaffolds.

of pharmacologists and organic chemists owing to their remarkable medicinal properties and their synthetically challenging heptacyclic structure. They have been examined as potential kinase inhibitors,[5] antiviral and antiallergic agents,[6–7] inhibitors of hepatitis C virus replication,[8–10] and antitumor agents;[11] however, only a few methods for their synthesis have been reported.[12] Therefore, a convenient strategy for efficiently constructing tetrahydro[1,4]diazepino[1,2-*a*]indole scaffolds is desirable.

Domino cyclization reactions triggered by transition-metal catalysis have been the subject of intense research in organic synthesis, and these one-pot processes can be used to construct polycyclic compounds rapidly. Recently, Fan et al. reported the use of a Pd-catalyzed domino reaction to construct 3,4-fused tricyclic azepino[5,4,3*cd*]indoles;[13] Lu et al. used a one-pot Pd^{II}-catalyzed reaction to construct cycloalkane-fused indoles (Scheme 1 a, b).[14] However, no Pd-catalyzed domino



Scheme 1. Pd-catalyzed domino cyclization to form fused indoles.

method for the synthesis of 1,2-fused tricyclic indoles has been reported. As part of our ongoing work on the use of domino cyclization reactions to prepare bioactive molecules, we have developed a method for the Pd-catalyzed domino synthesis of 1,2-fused tricyclic indoles from substituted 2,2,2-trifluoro-*N*-(2-iodophenyl)acetamides and *N*-protected (prop-2-yn-1-yl)acrylamides (Scheme 1 c). This method provides straightforward access to 1,2-fused tricyclic indoles.

To optimize the domino cyclization, we used 2,2,2-trifluoro-*N*-(2-iodophenyl)acetamide (**1 a**) and *N*-(prop-2-yn-1-yl)-*N*-tosylacrylamide (**2 a**) as model substrates (Table 1). Under the initial conditions, the target product **3 aa** was obtained in 67% yield (entry 1) and its structure was confirmed by X-ray diffraction.[15] The effect of the solvent was then investigated, and 1,4-dioxane was found to give the best yield of **3 aa** (82%, entry 3). When acetonitrile was used, the yield decreased to 38% (entry 2); most of **1 a** did not participate in the predominant reaction, which resulted in a complex mixture of side products. Increasing the temperature had a negative effect; the yield was only 25% when the reaction was conducted at 90 °C (entry 4). When lowering the temperature to 70 or 60 °C, the yield was only 72 and 50%, respectively (entries 5 and 6). Next, we investigated the effect of different bases. Both Cs_2CO_3 and Na_2CO_3 showed a lower reactivity than K_2CO_3 (entries 7

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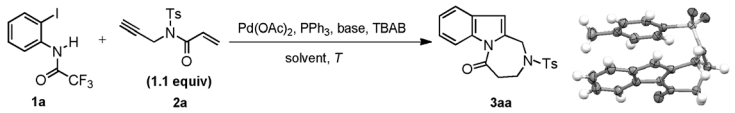
Table 1. Optimization of reaction conditions.[a]



Entry	$Pd(OAc)_2$ [mol%]	PPh_3 [mol%]	Base	Solvent	T [°C]	Yield [%][b]
1	20	80	K_2CO_3	DMF	80	67
2	20	80	K_2CO_3	CH_3CN	80	38
3	20	80	K_2CO_3	1,4-dioxane	80	82
4	20	80	K_2CO_3	1,4-dioxane	90	25
5	20	80	K_2CO_3	1,4-dioxane	70	72
6	20	80	K_2CO_3	1,4-dioxane	60	50
7	20	80	Cs_2CO_3	1,4-dioxane	70	52
8	20	80	Na_2CO_3	1,4-dioxane	70	trace
9	20	80	DBU	1,4-dioxane	70	38
10[c]	20	80	K_2CO_3	1,4-dioxane	70	trace
11	10	40	K_2CO_3	1,4-dioxane	80	81
12	5	20	K_2CO_3	1,4-dioxane	80	32

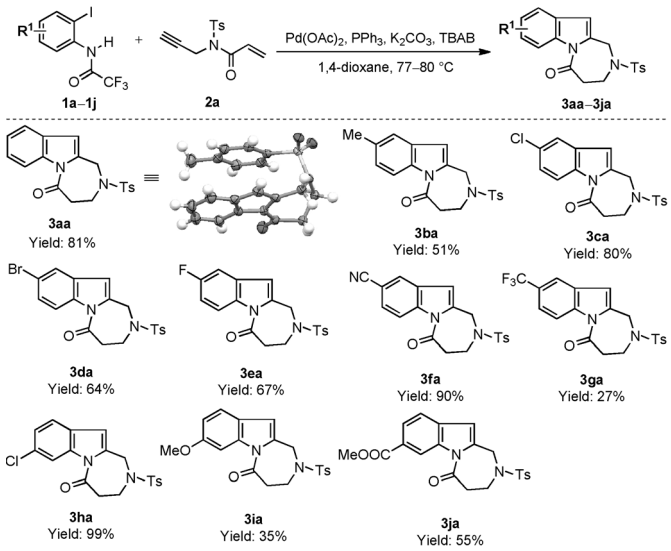
[a] Reaction conditions: **1a** (0.73 mmol), **2a** (1.1 equiv), base (2 equiv), TBAB (2 equiv) in solvent (25 mL) and H_2O (1 mL), unless otherwise noted. [b] Isolated yields. [c] TBAB was not added.

and 8). When the organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used, a portion of both substrates **1a** and **2a** remained, even after a prolonged reaction time (entry 9). Little or no reaction occurred in the absence of tetra-*n*-butylammonium bromide (TBAB; entry 10), which revealed the importance of the phase-transfer catalyst in the reaction.[16] Further optimization studies focused on the effect of the amounts of $Pd(OAc)_2$ and PPh_3. When the amounts of $Pd(OAc)_2$ and PPh_3 were decreased to 10 and 40 mol%, respectively (entry 11), the yield remained the same as compared to entry 3. However, when the amounts were further reduced, the yield decreased substantially (entry 12).

After having established the optimized conditions (Table 1, entry 11), the substrate scope was investigated. First, we evaluated substrates with various substituents on the benzene ring (**1a**–**1j**, Scheme 2) and found that electronic effects strongly influenced the reaction. Specifically, substrates with electron-donating groups, such as methyl and methoxyl, gave lower yields of the corresponding products (**3ba** and **3ia**); substrates with electron-withdrawing groups, such as fluoro (**3ea**), chloro (**3ca**, **3ha**), bromo (**3da**), and cyano (**3fa**), gave moderate to excellent yields. The yields decreased significantly when strongly electron-withdrawing groups, such as trifluoromethyl and carbonyl (**3ga** and **3ja**), were introduced. It is worth noting that the cyano and bromo functional groups on the benzene ring can be used to carry out further transformations.

Substrates **2b**–**2l** (Scheme 3) were synthesized to investigate the influence of the protecting group on the domino cyclization reaction. All compounds with a substituted benzenesulfonyl protecting group gave the expected products **3ab**--**3ai**. Compounds with an electron-donating group gave better yields than those with an electron-withdrawing group: the yields of **3aa**, **3ac**, **3ae**, and **3af** (81, 67, 75, and 73%, respectively) were much higher than the yields of **3ad** (9%) and **3ag**–**3ai** containing a halogen atom (35, 26, and 43%, respectively). When we changed the benzenesulfonyl protecting group to thiophen-2-ylsulfonyl, **3aj** was obtained in a moderate yield; compounds with a methyl and cyclopropyl sulfonyl protecting group gave the expected products **3ak** and **3al** in 44 and 51% yield. The reaction was strongly influenced by the steric effects of **2**; **3am** was obtained in only 14% yield when a methyl group was introduced to the terminal alkenyl of **2m**. Additionally, the octacyclic compound **3an** was obtained in 61% isolated yield. However, when a methylene group was added, the nonacyclic compound was not obtained.

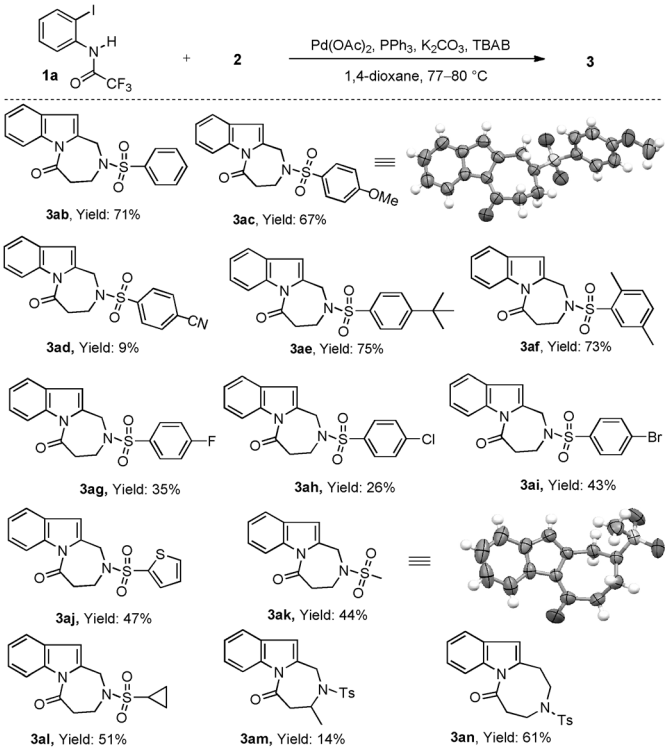
A proposed mechanism for this domino cyclization reaction is depicted in Scheme 4. The initial step involves a Pd-catalyzed Sonogashira coupling of **1a** and **2a** to form **4**.[17] Domino indole cyclization followed by an intramolecular transamidation reaction affords key intermediate **C** via **5** (path 1, route (1))[18–20] and subsequent Michael addition gives **3aa**. There is another possible pathway to **3aa**: **4** can be converted to **6** through an intermolecular



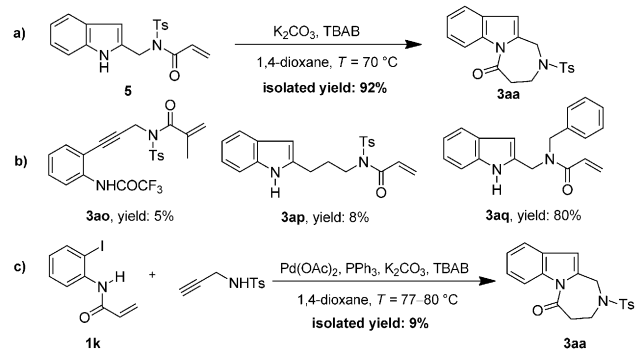
Scheme 2. Synthesis of tetrahydro[1,4]diazepino[1,2-*a*]indoles. Reaction conditions: **1** (0.73 mmol), **2** (0.77 mmol), TBAB (1.46 mmol), K_2CO_3 (1.46 mmol), $Pd(OAc)_2$ (10 mol%), PPh_3 (40 mol%), and H_2O (1 mL) in 1,4-dioxane (25 mL) at 77–80 °C for 4–10 h. Isolated yields are reported.

transamidation reaction, which occurs prior to the indole cyclization, and then **C** is formed via indole cyclization of intermediate **6** (path 2).

To determine whether path 1 or path 2 is more likely, we conducted several control experiments. First, we prepared the proposed intermediate **5** by using reported methods[21–23] and subjected it to alkaline conditions in the absence of a Pd catalyst (Scheme 5a). To our delight, the expected cyclization proceeded smoothly to give **3aa** in 92% yield, which proved that **5** is an intermediate in the domino reaction. It is worth noting that **3aa**′ was not obtained either from **5** or from **1a**, which



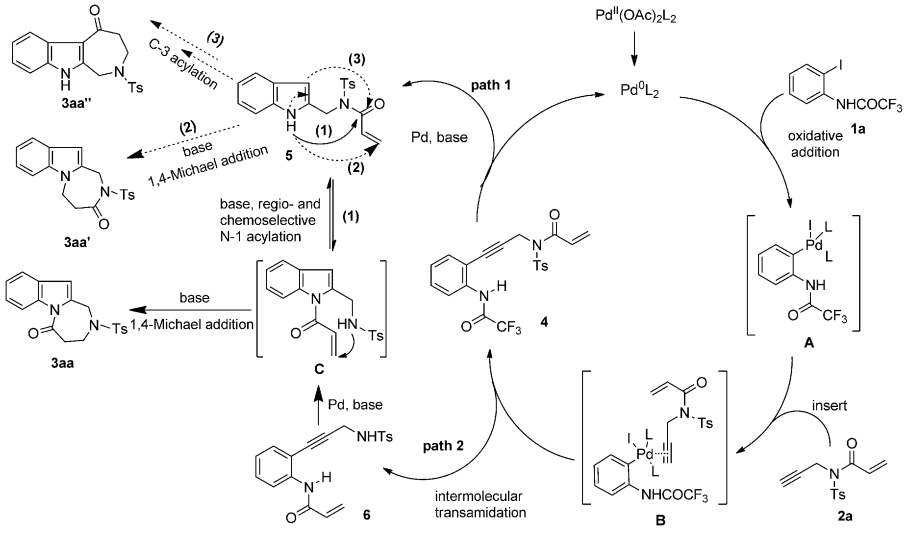
Scheme 3. Synthesis of tetrahydro[1,4]diazepino[1,2-*a*]indoles and hexahydro[1,5]diazocino[1,2-*a*]indoles. Isolated yields are reported.



Scheme 5. Control experiments.

to the domino cyclization conditions (Scheme 5c), **3aa** was obtained in 9% yield; this suggests that path 2 cannot be ruled out.

In summary, we developed a Pd-catalyzed domino route for the synthesis of tetrahydro[1,4]diazepino[1,2-*a*]indoles by using simple substituted 2,2,2-trifluoro-*N*-(2-iodophenyl)acetamides and *N*-protected (prop-2-yn-1-yl)acrylamides as starting materials. This method provides straightforward access to 1,2-fused tricyclic indoles. On the basis of corresponding experiments and X-ray crystal structures of products **3**, we propose a mechanism involving a Pd-catalyzed Sonogashira coupling, indole cyclization, regio- and chemoselective N-1 acylation, and 1,4-Michael addition. Further studies on the application of this domino route are in progress in our laboratory.



Scheme 4. Proposed mechanism.

suggests that a 1,4-Michael addition (Scheme 4, path 1, route (2)) does not occur under our reaction conditions; in addition, the C-3 acylation product **3aa''** (path 1, route (3)) was not obtained. These results indicate that the acylation reaction of **5** to afford **C** exhibits excellent chemo- and regioselectivity. Additionally, **3ao**, **3ap**, and **3aq** (Scheme 5b) were separated from product mixtures that were obtained from the domino reaction of **1a** with **2**. The above results indicate that path 1 is the proposed pathway. However, when substrate **1k** and 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide were subjected

Experimental Section

Experimental details and additional data can be found in the Supporting Information.

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Keywords: chemoselectivity · cyclization · domino reactions · indoles · palladium · regioselectivity

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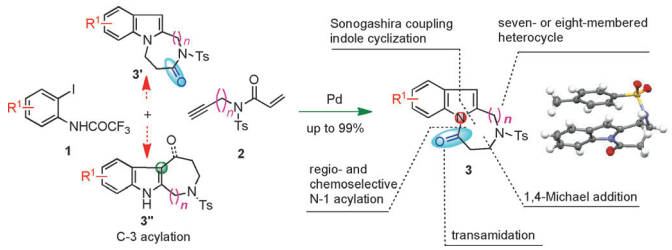

Domino route: A concise method for the synthesis of 1,2-fused tricyclic indole scaffolds by domino cyclization is reported. This method provides straightforward access to tetrahydro[1,4]diazepino[1,2-*a*]indole and hexahydro[1,5]diazocino[1,2-*a*]indole scaffolds (see figure).

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