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# A Domino Amidation Route to Indolines and Indoles: Rapid Syntheses of Anhydrolycorinone, Hippadine, Oxoassoanine, and Pratosine

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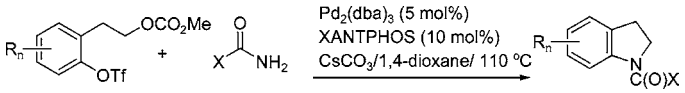
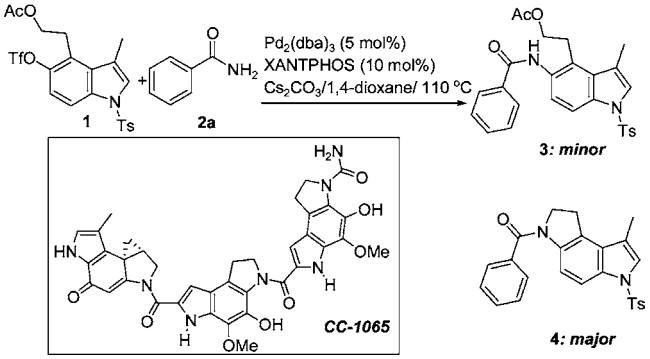
## ABSTRACT




**When subjected to palladium-catalyzed amidation conditions, 2-triflyloxy phenethyl carbonates undergo, in addition to the expected aryl cross-coupling, an additional amidation with net displacement of the carbonate. The result is a one-step synthesis of indolines which may be oxidized to indoles. The utility of the procedure is illustrated by the two- or three-step syntheses of anhydrolycorinone, hippadine, oxoassoanine, and pratosine.**

The recent development of palladium-catalyzed aryl C−N cross-coupling reactions has revolutionized organic synthesis.[1] The more recent use of palladium-catalyzed C−N bond-forming reactions in domino processes has allowed for the efficient construction of nitrogen-containing heterocycles, such as indolines and indoles.[2]

During studies directed toward the synthesis of CC-1065 and related compounds, we explored the installation of the dihydropyrrole subunits via the amidation of a 5-triflyloxy-indole such as **1** with benzamide **2**. The intention was to convert the acetate in **3** to a good leaving group and effect the ring formation to **4** in a nucleophilic manner. We were surprised to isolate the pyrroloindole **4** as the major product from the cross-coupling reaction and **3**, especially since the same reaction involving halides in place of the acetoxy moiety (a poorer leaving group) led to decomposition. We decided to explore this unusual reaction since the palladium-catalyzed "stitching" of a nitrogen atom to prepare indolines (and possibly indoles) would be a useful method for the synthesis of alkaloids and other indole containing targets.




Scheme 1 shows an optimization study in which the aliphatic "leaving group" was varied and the catalyst loading was probed for its lower limit. While the chloride **5a** and bromide **5b** produced appreciable amounts of the desired compound, the yield was low, and extensive decomposition was observed. The iodide **5c** failed to produce identifiable products. The mesylate **5d** produced, along with the desired

(1) For reviews, see: (a) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (c) Hartwig, J. F. *Modern Arene Chemistry* **2003**, 107.

(2) For recent examples, see: (a) Poondra, R. R.; Turner, N. J. *Org. Lett.* **2005**, *7*, 863. (b) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906. (c) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (d) Aoki, K.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 3068.

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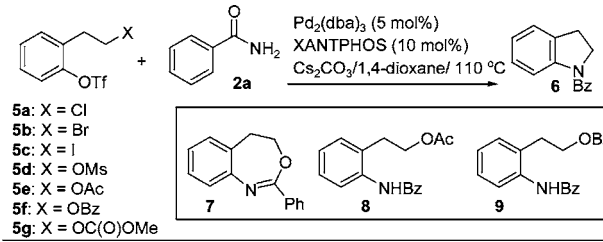
**Scheme 1.** Variation of Leaving Group and Catalyst Loading




| entry | substrate | $Pd_2(dba)_3$ (mol%) | XANTPHOS (mol%) | products (yield) |
|---|---|---|---|---|
| 1 | **5a** | 10 | 20 | **6** (35%) |
| 2 | **5b** | 10 | 20 | **6** (34%) |
| 3 | **5c** | 10 | 20 | decomp. |
| 4 | **5d** | 10 | 20 | **6** (44%) + **7** (10%) |
| 5 | **5e** | 10 | 20 | **6** (51%) + **8** (41%) |
| 6 | **5f** | 10 | 20 | **6** (73%) + **9** (22%) |
| 7 | **5g** | 10 | 20 | **6** (98%) |
| 8 | **5g** | 5 | 10 | **6** (98%) |
| 9 | **5g** | 2.5 | 5 | **6** (98%) |
| 10 | **5g** | 1.25 | 2.5 | **6** (82%) |
| 11 | **5g** | 0.5 | 1 | **6** (25%) |

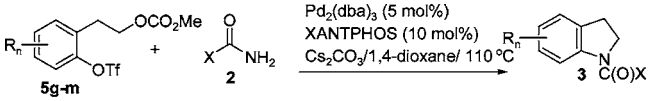
indoline **6**, the heterocycle **7** in which participation by the amide oxygen occurred. The acetate **5e** and benzoate **5f** gave both the indoline **6** and the uncyclized amidation products **8** and **9**. The carbonate **5g** proved to be the ideal substrate giving a near-quantitative yield of **6** with catalyst loadings of as low as 2.5 mol %. Only when the loading was dropped to 0.5 mol % did the yield drop to an unacceptable level.

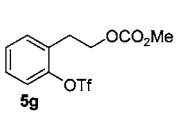
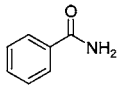
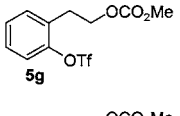
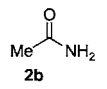
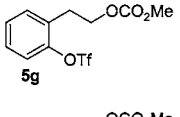
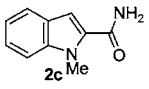
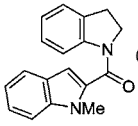
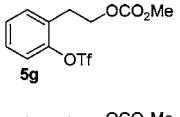
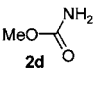
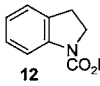
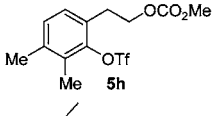
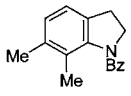
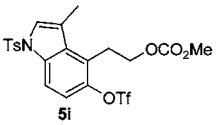
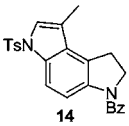
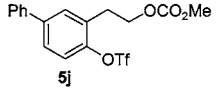
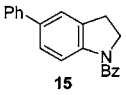
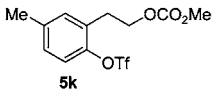
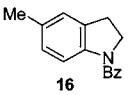
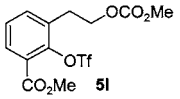
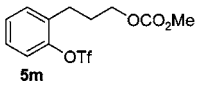
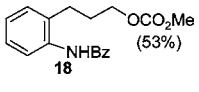
To investigate substrate scope using optimized conditions, a series of compounds bearing an aryl triflyloxy group and a pendant alkyl carbonate was subjected to the domino amidation sequence (Table 1). Several examples are worthy of note. In all cases, the aryl amidation was seen to occur first, and if the reaction was stopped an early stage, the uncyclized anilide could be isolated implying that the N-arylation is a distinct event and is followed by an intramolecular N-alkylation. The amido component seems to be general (entries 1−4); benzamide acetamide, *N*-methylindole-2-carboxamide, and methyl carbamate gave good results. Substitution on the aryl moiety of the triflate component was tolerated, although both examples which had substitution ortho to the triflyloxy group gave diminished yields (entries 5 and 9). Surprisingly, extension of the alkyl chain by one carbon in the hopes of preparing tetrahydro quinolines met with little success (entry 10). Although a trace amount of the cyclized material was isolated, the major product was the uncyclized material **18**, in which only aryl amidation was observed.

While the amidation of the aryl ring was certainly expected, the subsequent cyclization puzzled us, especially since the best substrates by far were the carbonates and not alkyl halides.[3] It occurred to us that the cyclization may also be a palladium-mediated event and furthermore that the cyclization was proceeding through a hydroamination of a

(3) The alkylation of anilides with carbonates is very rare but known. See, for example: Selva, M.; Tundo, P.; Perrosa, A. *J. Org. Chem.* **2001**, *66*, 667 and references therein.

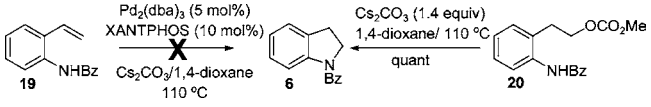
**Table 1.** Substrate Scope[4]




| entry | substrate | amide | time (h) | products (yield) |
|---|---|---|---|---|
| 1 |  |  | 22 |  (98%) |
| 2 |  |  | 45 |  (85%) |
| 3 |  |  | 46 |  (83%) |
| 4 |  |  | 40 |  (71%) |
| 5 |  | 2a | 45 |  (52%) |
| 6 |  | 2a | 21 |  (96%) |
| 7 |  | 2a | 22 |  (92%) |
| 8 |  | 2a | 46 |  (75%) |
| 9 |  | 2a | 45 |  (42%) |
| 10 |  | 2a | 22 |  (53%) |

styrene. This would explain the failure of the formation of the six-membered ring (Table 1, entry 10). However, treatment of **19** (Scheme 2) under the optimized reaction conditions for indoline formation resulted in almost complete recovery of starting material, indicating that a styrene was not a likely intermediate in the indoline formation.

**Scheme 2.** Probing the Cyclization Step



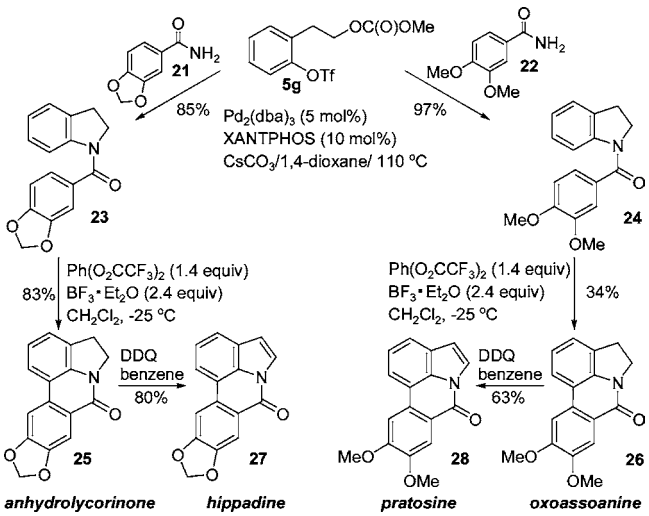

To determine whether the cyclization of the benzanilide to the *N*-benzoylindoline was a palladium-catalyzed reaction,

the amidocarbonate **20** (Scheme 2) was prepared. *While treatment of **20** under the palladium-catalyzed conditions shown in Scheme 1 resulted in near-quantitative conversion to **6**, the same results were obtained when the palladium catalyst and phosphine were removed from the reaction.* Clearly, the second process (the intramolecular amidation) is not a palladium-catalyzed process and is most likely a nucleophilic displacement (albeit an unusual one with a carbonate leaving group) promoted by the $Cs_2CO_3$.[5]

With an optimal procedure for the formation of indolines from the triflyloxy carbonates, we undertook to showcase this methodology with the synthesis of several simple Amaryllidaceae pyrrolophenanthridone natural products (Scheme 3).[6] Treatment of **5g** with piperonylamide **21** or veratramide **22** under the standard conditions gave indolines **23** and **24** in 85 and 97% yields, respectively. Oxidative cyclization of **23** under the influence of phenyliodo bistrifluoroacetate (PIFA)[7] gave anhydrolycorinone **25** in 83% yield.[8] Similarly, oxidation of **24** with iodosobenzene gave oxoassoanine in 47% yield. Treatment of **25** and **26** with freshly recrystallized DDQ in dry benzene gave hippadine **27** and pratosine **28** in 80 and 63% yields.

In conclusion, we have developed a convenient, one-pot, domino $sp^2-sp^3$ amidation for the formation of indolines and indoles from *o*-triflyloxyphenethyl carbonates. This sequence involves, as the individual components, a palladium-catalyzed amidation of the aryl triflate followed by a unique displacement of the aliphatic carbonate. The protocol was employed in the rapid synthesis of the natural products anhdrolycorinone, hippadine, pratosine, and oxoassoanine in two or three steps from the triflyloxy carbonate.

**Scheme 3.** Syntheses of Pyrrolophenanthridone Natural Products

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**Supporting Information Available:** Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) For the reaction of **5g** with **2a**, **2b**, and **2d**, 1.5 equiv of amide was used. For the reaction of **5g** with **2a**, **2b**, and **2c**, 2.5 mol % of $Pd_2(dba)_3$ and 5 mol % of XANTPHOS were used.

(5) Treatment of **20** with DBU, NaH, and $^t$-BuOK did not lead to cyclization; however, $K_2CO_3$ and $Na_2CO_3$ were effective in the conversion of **20** to **6**.

(6) (a) Anhydrolycorinone and hippadine: Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1981**, *20*, 2003. (b) Oxoassoanine: Llabres, J. M.; Viladomat, F.; Bastida, J.; Codina, C.; Rubiralta, M. *Phytochemistry* **1986**, *25*, 2637. (c) Pratosine: Ghosal, S.; Saini, K. S.; Frahm, A. W. *Phytochemistry* **1983**, *22*, 2305.

(7) Lead references for the PIFA-mediated oxidative biphenyl formation: (a) Moreno, I.; Tellitu, I.; Etayo, J.; SanMartín, R.; Domínguez, E. *Tetrahedron* **2001**, *57*, 5403. (b) Kita, Y.; Egi, M.; Okijama, A.; Ohtsubo, M.; Takada, T.; Tohma, H. *Chem. Commun*. **1996**, 1481.

(8) If oxidation was performed with PIFA, a dimeric compound stemming from biaryl coupling was isolated in significant amounts.