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# Pd(II)-Catalyzed Intramolecular Tandem Olefin Amidation/C−H Activation Protocol for the Syntheses of the Protoberberine Class of Natural Products

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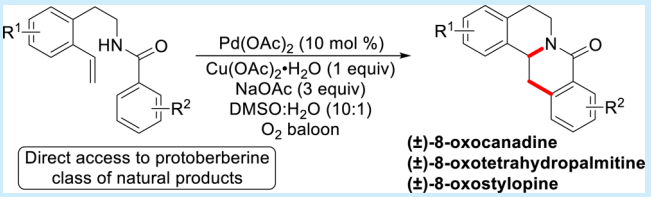
Supporting Information

**ABSTRACT:** A Pd(II)-catalyzed intramolecular tandem olefin amidation/C−H activation protocol has been developed for the synthesis of an 8-oxoprotoberberine core. It was successfully applied for the syntheses of (±)-8-oxocanadine, (±)-8-oxotetrahydropalmitine, and (±)-8-oxostylopine, which can be easily converted to the respective protoberberine natural products. The short synthetic route demonstrated would be useful for the synthesis of a large number of natural products and their analogues featuring a protoberberine scaffold.




Protoberberine alkaloids are a subdivision of natural products containing an isoquinoline skeleton. They are secondary metabolites having significant biological activities because of their ability to bind or insert in DNA.[1] Isolated from a wide range of plants, all members of the protoberberine class feature a 5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]-isoquinoline moiety, typically functionalized with hydroxy, methoxy, or methylenedioxy substituents (Figure 1).[1,2] The parent compound, berberine, is the most widely studied alkaloid and exhibits antifungal, antibacterial, anti-inflammatory, antimalarial, antidiabetic, and anticancer activities.[3] This family

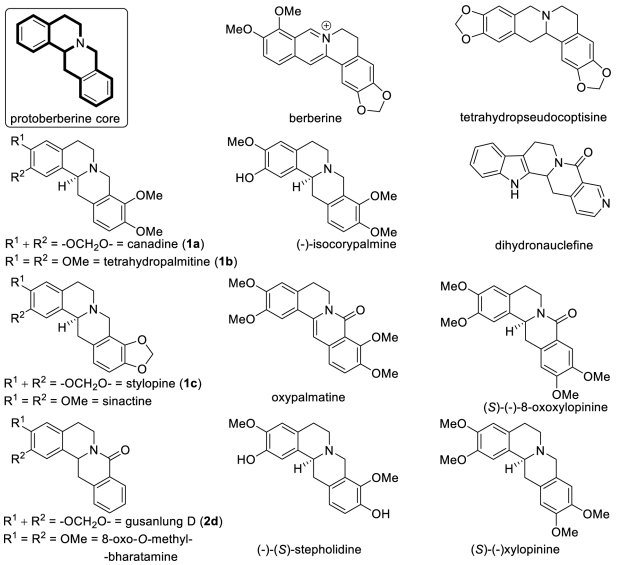



**Figure 1.** Selected natural products containing a protoberberine core.[1−3]

of natural products has acquired immense attention in the scientific community for their synthesis by various approaches, including transition-metal-catalyzed methods for their construction.[1−3] Pd-catalyzed direct aromatic carbonylation using CO as the carbon source in the synthesis of 8-oxoberberines was developed by Orito and co-workers.[2e,f,i] Other Pd-catalyzed methods such as enolate arylation[1] and intramolecular Heck-type reaction[2g] were also utilized. Difunctionalization of olefins is a powerful strategy in organic synthesis for the construction of complex alkaloid natural products.[4b]

We envisioned that an intramolecular tandem C−N/C−C bond formation (carboamidation) of internal olefins by C−H activation could be an interesting method to construct an isoquinoline core in the synthesis of protoberberine alkaloids. In this context, the literature survey revealed that amino-arylation reactions of olefins/alkynes are known, which requires aryl halides as a coupling partner.[4] Tandem Pd-catalyzed intramolecular amidation of alkenes followed by intermolecular C−H activation of arenes was reported by Michael et al. in 2009 (Figure 2, eq 1).[5] Several examples of intermolecular tandem C−C/C−N bond formation also have been reported.[4,6,7] Directing-group (*N*-OPiv amide)-specific, rhodium-catalyzed intramolecular amidoarylation of olefins was reported by Rovis et al. (Figure 2, eq 2).[8] The *N*-OPiv amide also acts as a stoichiometric oxidant, which makes the catalytic ring closure a redox-neutral process. There are few examples known in the literature wherein difunctionalization of internal alkynes was achieved by a tandem amidation/C−H activation sequence (Figure 2, eq 3).[9] However, to the best of our knowledge, such difunctionalization of internal olefins to access an isoquinolinone core of protoberberine alkaloids is not known until now (Figure 2, eq 4). In this report, we describe a

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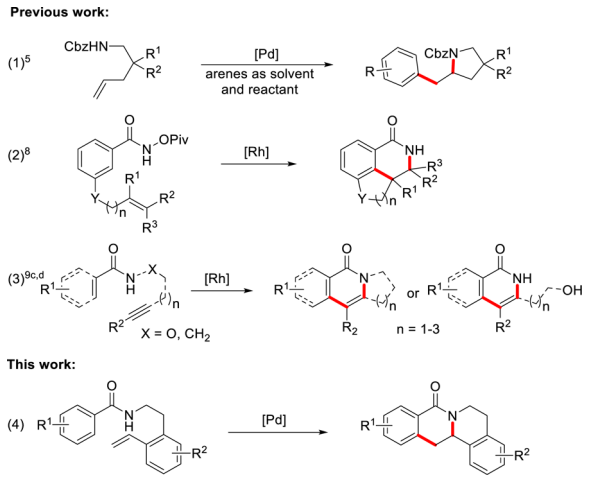
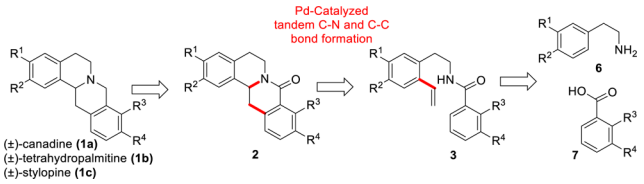



**Figure 2.** Difunctionalization of olefins and alkynes.

unique intramolecular Pd-catalyzed tandem oxidative olefin amidation/C−H activation protocol for the synthesis of a protoberberine class of natural products.

Our retrosynthetic plan is shown in Scheme 1. The protoberberine natural products **1a−c** can be easily accessed by reduction of its corresponding 8-oxoberberine derivative **2**, which can be obtained from vinyl amide **3** using the proposed Pd-catalyzed tandem olefin amidation/C−H activation protocol. Vinyl amide **3** can be generated from the corresponding aryl ethyl amine **6** and carboxylic acid **7** in three simple steps: amide coupling, iodination, and Stille coupling.

**Scheme 1. Retrosynthetic Analysis of Protoberberines**




The synthesis began with the coupling of the corresponding aryl ethyl amines **6a**/**6b** and carboxylic acids **7a**/**7b** using EDC·HCl[10] to obtain amides **5a−c** in good to moderate yields, and amide **5d** was synthesized by coupling amine **6a** and benzoyl chloride in moderate yield (Scheme 2). Amides **5a−d** were then treated with iodine and silver triflate[11] in a dark atmosphere to furnish iodoamides **4a−d** in very good yields and excellent regioselectivity. Iodoamides **4a−d** were further treated with tributyl(vinyl)stannane under Stille coupling conditions[10] catalyzed by $Pd_2(dba)_3$ and triphenylarsane as a ligand to obtain vinylamides **3a−d** in very good to excellent yields.

Various catalysts, oxidants, and reaction conditions were screened on vinylamide **3a** for the expected tandem amidation/C−H activation reaction to obtain an optimized protocol (Table 1). The first reaction toward this goal used catalytic $Pd(OAc)_2$ and $Cu(OAc)_2$ in the presence of base/additive AgOAc at 110 °C in DMF, which gave the expected product, though in low yield (entry 1). The base/additive AgOAc was replaced with NaOAc, which enhanced the yield by 10% (entry 2). Variation in metal catalysts or solvents did not show formation of expected product (entries 3−5). Interestingly, the change in solvent from DMF to DMSO and performing the reaction under oxygen atmosphere showed improvement in yield to 35% along with 30% starting material recovery (entries 6 and 7). After variations in additives (entries 8−11), we found an optimized reaction condition (entry 12), wherein the highest

**Scheme 2. Synthetic Route for 8-Oxoberberines**

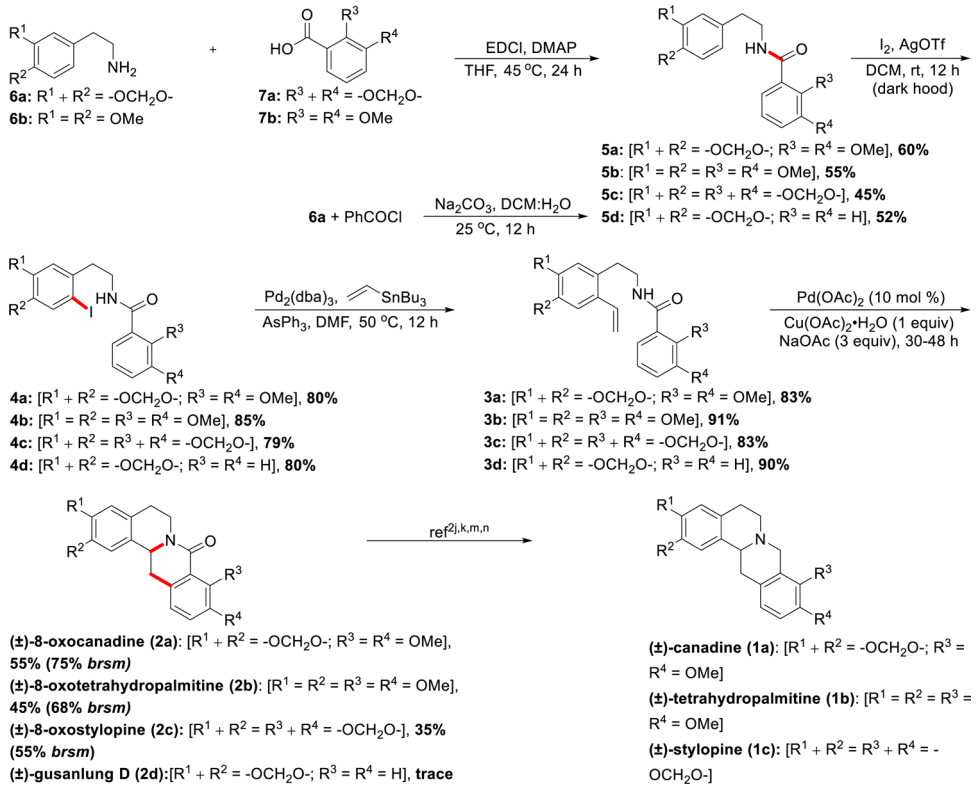





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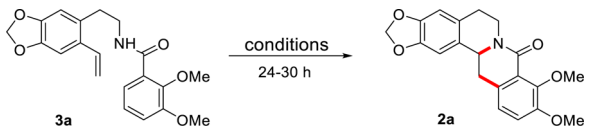
**Table 1. Optimization Studies**[a]




| entry | catalyst (mol %) | oxidant (equiv) | additive (equiv) | solvent/temp | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2$ (0.2) | AgOAc (2) | DMF/110 °C | 15 |
| 2 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2$ (0.2) | NaOAc (2) | DMF/110 °C | 25 |
| 3 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2·H_2O$ (2) | NaOAc (2) | *t*-amyl alcohol/115 °C | – |
| 4 | $[RhCp^*Cl_2]_2$ (2.5) | $Cu(OAc)_2$ (0.2) | AgOAc (1.5) | $CH_3CN$/110 °C | – |
| 5 | $[RuCl_2(p\text{-cy})]_2$ (5) | $Cu(OAc)_2·H_2O$ (2) | $AgSbF_6$ (0.2) | 1,4-dioxane/100 °C | – |
| 6 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2$ (0.2) | NaOAc (2) | DMSO/100 °C | 30 |
| 7 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2$ (2), $O_2$ | NaOAc (2) | DMSO/100 °C | 35 |
| 8 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2·H_2O$ (2), $O_2$ | KOAc (2) | DMSO/100 °C | 25 |
| 9 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2·H_2O$ (2), $O_2$ | NaOAc (2), PivOH (0.4) | DMSO/100 °C | 40 |
| 10 | $Pd(OAc)_2$ (10) | $O_2$ | NaOAc (2), PivOH (0.4) | DMSO/100 °C | – |
| 11 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2·H_2O$ (2), $O_2$ | NaOAc (2), PivOH (0.4) | DMSO/$H_2O$ (9:1)/100 °C | 45 |
| **12**[b] | **$Pd(OAc)_2$ (10)** | **$Cu(OAc)_2·H_2O$ (1), $O_2$** | **NaOAc (3)** | **DMSO/$H_2O$ (10:1)/100 °C** | **55 (75% brsm)** |
| 13 | $[RhCp^*Cl_2]_2$ (2.5) | $Cu(OAc)_2·H_2O$ (1), $O_2$ | NaOAc (3) | DMSO/$H_2O$ (10:1)/100 °C | – |
| 14 | $Pd(TFA)_2$ (10) | $Cu(OAc)_2·H_2O$ (1), $O_2$ | NaOAc (3) | DMSO/$H_2O$ (10:1)/100 °C | 42 |
| 15 | $PdCl_2$ (10) | $CuCl_2·2H_2O$ (1) | NaOAc (3) | DMSO/$H_2O$ (10:1)/100 °C | 20 |
| 16 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2·H_2O$ (1), $O_2$ | NaOAc (3) | DMAc/$H_2O$ (9:1)/100 °C | 33 |
| 17 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2·H_2O$ (1), $O_2$ | NaOAc (3) | DMAc/DMSO (9:1)/100 °C | 35 |

[a]All reactions were performed on 18 mg (0.05 mmol) scale of vinylamide **3a**. [b]DMSO/$H_2O$ (0.3:0.03 mL).

possible yield of product (±)-8-oxocanadine (**2a**, 55%, 75% brsm) was obtained. However, further modifications (entries 13−17) or variation in catalyst loading did not show improvement in the yield. Application of the developed protocol on vinylamides **3b** and **3c** provided cyclized products (±)-8-oxotetrahydropalmitine (**2b**) and (±)-8-oxostylopine (**2c**) in 45% (68% brsm) and 35% (55% brsm) yields, respectively (Scheme 2). The analytical and spectral data of 8-oxoberberines **2a−c** are consistent with the reported data.[2e] Their transformation to the corresponding natural products (±)-canadine (**1a**), (±)-tetrahydropalmitine (**1b**), and (±)-stylopine (**1c**) is well-documented in the literature.[2j,k,m,n] Unfortunately, vinylamide **3d**, when subjected to our developed protocol, showed formation of only a trace (ESI-HRMS) amount of natural product gusanlung D (**2d**) and most of the starting material remained unreacted. When the reaction temperature was increased to 120−140 °C, decomposition of vinylamide **3d** was observed.

A proposed mechanism for the intramolecular carboamidation protocol developed herein is depicted in Figure 3. The

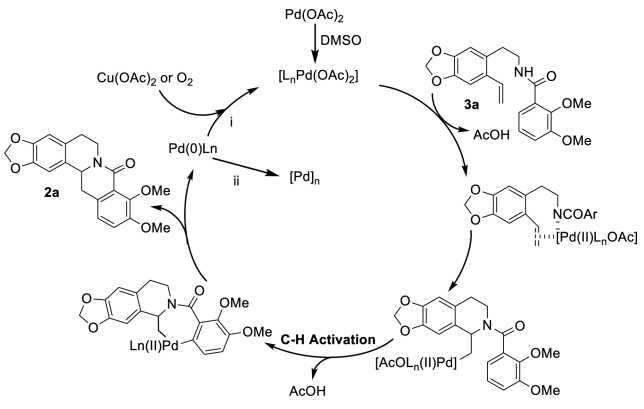



**Figure 3.** Proposed mechanism for the intramolecular carboamidation.

active catalyst might be formed by the coordination of DMSO with Pd(II), which catalyzes further transformations.[12] The intrinsically unstable form of the catalyst "$Pd(0)L_n$" generated in the reaction mixture is reoxidized (Figure 3i) by the oxidant to complete the catalytic cycle; however, a competing reaction, which deactivates Pd(0) to catalytically inactive palladium black,[13] might be the reason behind the incomplete conversion (Figure 3ii).

In summary, a novel Pd(II)-catalyzed approach for the synthesis of a protoberberine core was developed. The two new bonds, C−N and C−C, have been formed in a single step by an intramolecular tandem "amidation/C−H activation" sequence. Short and efficient syntheses of (±)-8-oxocanadine, (±)-8-oxotetrahydropalmitine, and (±)-8-oxostylopine were achieved by implementing this novel protocol as a key step. Currently, we are working on the total synthesis of other natural alkaloids in this class using the developed protocol.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01868.

Experimental procedures, spectral and analytical data, and copies of NMR spectra of all compounds (PDF)

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### Notes

The authors declare no competing financial interest.



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