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Palladium-Catalyzed Intramolecular δ-Lactam Formation of Aryl Halides and Amide-Enolates: Syntheses of Cherylline and Latifine

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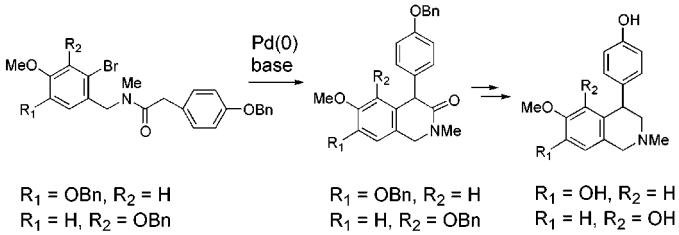
ABSTRACT



Palladium-catalyzed intramolecular carbon–carbon bond formation of aryl halides and amide-enolates gave 4-arylisoquinoline derivatives in good yields, which were further converted into the isoquinoline alkaloids cherylline and latifine.

The palladium-catalyzed coupling reaction of aryl halides or vinyl halides and enolates is a promising procedure to construct the carbon framework of polycyclic compounds, including natural products.[1] Recently, a number of modifications of this strategy were developed to prove their versatility and utility in the synthesis of structurally interesting organic compounds. However, application of this methodology to the synthesis of natural products, especially to isoquinoline alkaloids, has received little attention. In 1990, Piers successfully utilized this reaction in the synthesis of the diterpene crinipellin B.[2] Moreover, Mann employed this type of coupling reaction for the synthesis of the basic skeleton of huperzine A,[3] and Bonjoch also reported the construction of bridged aza-bicyclic compounds as potential starting materials of indole alkaloids,[4] independently.

In our continuing work on the synthesis of isoquinoline alkaloids, we were interested in the synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloids[5] cherylline (**1**) and latifine (**2**) by employing Pd-catalyzed intramolecular coupling of aryl halides and amide-enolates,[1b] because the compounds having such ring systems would be expected to exhibit potential biological activities of medicinal interest.[6]

(1) For the Pd-catalyzed intramolecular coupling of aryl halides and enolates, see: (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581−7582. (b) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546−6553. (c) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355−2358. For the Pd-catalyzed intermolecular coupling of aryl halides and enolates, see: (d) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370 and references therein.

(2) (a) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454−3455. (b) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11−13.

(3) Foricher, Y.; Mann, J. *Tetrahedron Lett.* **2000**, *41*, 2007−2009.

(4) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225−2228.

(5) For the recent syntheses of cherylline and latifine, see: (a) Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2447−2453. (b) Kobayashi, S.; Tokumoto, T.; Iguchi, S.; Kihara, M. *J. Chem. Res., Synop.* **1986**, 280−281. (c) Katakawa, J.; Yoshimatsu, H.; Yoshida, M.; Zhang, Y.; Irie, H.; Yajima, H. *Chem. Pharm. Bull.* **1988**, *36*, 3928−3932. (d) Cuevas, J. C.; Snieckus, V. *Tetrahedron Lett.* **1989**, *30*, 5837−5840. (e) Couture, A.; Deniau, E.; Woisel, P.; Grandclaudon, P.; Carpentier, J. F. *Tetrahedron Lett.* **1996**, *37*, 3697−3700. (f) Couture, A.; Deniau, E.; Lebrun, S.; Grandclaudon, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 789−794 and references therein.

(6) (a) Kohli, J. D.; Goldberg, L. I. *J. Pharm. Pharmacol.* **1980**, *32*, 225−226. (b) Poat, J. A.; Woodruff, G. N.; Watling, K. J. *J. Pharm. Pharmacol.* **1978**, *30*, 495−497. (c) Costall, B.; Naylor, R. J. *J. Pharm. Pharmacol.* **1978**, *30*, 514−516. (d) Jacob, J. N.; Nichols, D. E.; Kohli, J. D.; Glock, D. *J. Med. Chem.* **1981**, *24*, 1013−1015.

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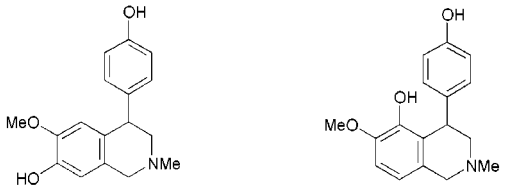


Figure 1. Structures of cherylline (**1**) and latifine (**2**).

The formation of lactam rings by this methodology has already been reported by Hartwig and co-workers to give the desired products (Figure 2).[1b] They, however, mentioned

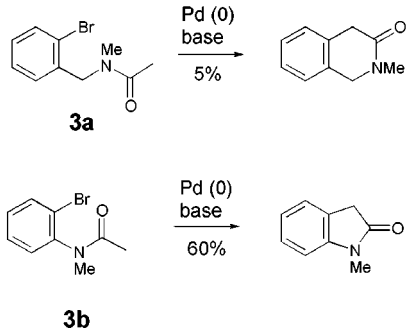


Figure 2. Pd-catalyzed lactam formation.

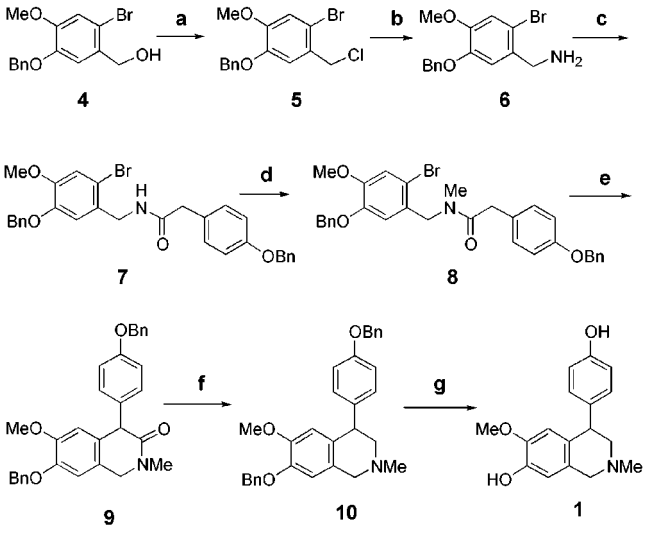
that reaction of **3a** gave δ-lactam in poor yield, although γ-lactam formation of **3b** proceeded in good yield. We considered that the low-yielding six-membered lactam formation might be attributed to the weak acidity of the methyl proton of an acetamide group or the instability of the generated enolate.

Thus, we prepared amide **8** having a methylene group with relatively strong acidity as follows (Scheme 1). Alcohol **4** was converted into amine **6** in four steps, via chloride **5**, by adopting Cossy's procedure with slight modifications.[7] Schotten−Baumann reaction of amine **6** with *p*-benzyloxyphenylacetyl chloride gave amide **7**, which was further alkylated with methyl iodide to provide the desired amide **8** as a mixture of rotamers of the amide group in a ratio of ca. 3:2. The Pd-catalyzed intramolecular coupling reaction of **8** in the presence of 0.1 equiv of $Pd(dba)_2$, 0.15 equiv of dppe, and 1.5 equiv of ^{t}BuOK in refluxing dioxane proceeded smoothly to give six-membered lactam **9** in 81% yield, together with a trace amount of a debromo compound. When the reaction was carried out in the presence of Cs_2CO_3 as the base, the yield of δ-lactam was much decreased (>10%).

Lactam **9** thus prepared was further transformed to the natural product as follows. Reduction of δ-lactam **9** with

(7) Cossy, J.; Tresnard, L.; Pardo, D. G. *Tetrahedron Lett.* **1999**, *40*, 1125−1128.

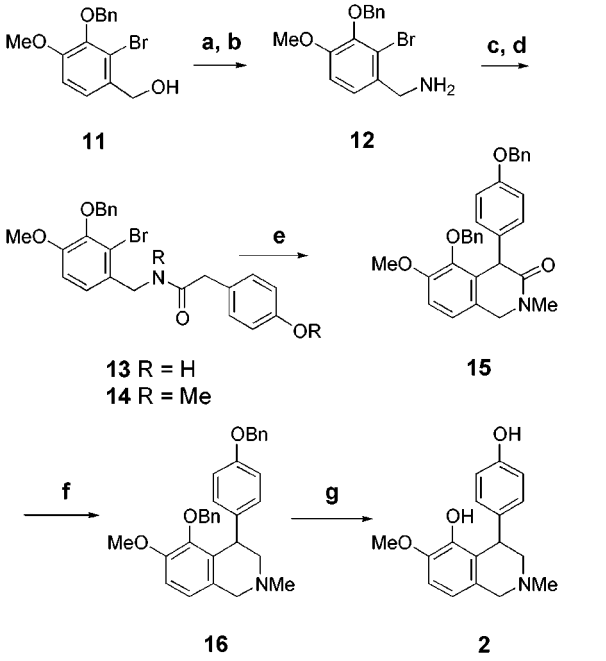
Scheme 1. Synthesis of Cherylline[a]



[a] (a) $SOCl_2$, benzene, reflux, 100%; (b) (i) NaN_3, DMF; (ii) Ph_3P, THF; (iii) H_2O, reflux, 89% from **5**; (c) *p*-benzyloxyphenylacetyl chloride, $NaHCO_3$, Et_2O, 87%; (d) NaH, DMF, MeI, 93%; (e) ^{t}BuOK, $Pd(dba)_2$, dppe, dioxane, 100 °C, 81%; (f) BMS, THF, 65 °C, 91%; (g) H_2, Pd−C, EtOH, 65 °C, 68%.

borane-dimethyl sulfide (BMS) complex[8] provided di-*O*-benzylcherylline **10**, mp 144−145 °C (lit.[9] mp 144−145 °C), which was identical with the authentic sample, previously

Scheme 2. Synthesis of Latifine[a]



[a] (a) $SOCl_2$, benzene, reflux, 100%; (b) (i) NaN_3, DMF; (ii) Ph_3P, THF; (iii) H_2O, reflux, 90% from **5**; (c) *p*-benzyloxyphenylacetyl chloride, $NaHCO_3$, Et_2O, 87%; (d) NaH, DMF, MeI, 77%; (e) ^{t}BuOK, $Pd(dba)_2$, dppe, dioxane, 100 °C, 54%; (f) BMS, THF, reflux, 61%; (g) H_2, EtOH, Pd−C, 65 °C, 85%.

prepared by us.[9] Finally, compound **10** was converted to cherylline **1** by hydrogenolysis over 10% palladium on carbon in 68% yield.

The Pd-catalyzed intramolecular δ-lactam formation was extended to the synthesis of latifine **2** by employing essentially the same procedure as described above (Scheme 2). The requisite *N*-methylamide **14** was prepared from alcohol **11** in six steps, via amine **12** and amide **13**, as a mixture of rotamers in a ratio of ca. 1:1. Attempted cyclization of **14** with $Pd(dba)_2$ under similar reaction conditions as above gave the desired δ-lactam **15**, in 54% yield, together with the debromo compound (20%).

Although the coupling yield was lower than that for cherylline, probably as a result of the presence of steric hindrance with the benzyl group at the *ortho*-position to the reaction site, the δ-lactam **15** was further converted to latifine **2**, mp 213−215 °C (lit.[5a] mp 212−215 °C), by reduction with borane-dimethyl sulfide complex, in 61% yield, followed by hydrogenolysis[5a] of the resulting amine **16**, successfully. Again, the spectroscopic data of the synthetic compound **2** are identical with those reported.[5a]

We also attempted a chiral induction in the coupling of **8** under similar reaction conditions using $Pd(dba)_2$, ^{t}BuOK, and chiral ligand (*S*)-BINAP in refluxing dioxane; however, the desired compound **9** was isolated in 42% yield with only 8% ee (based on the HPLC analysis using the chiral column OD), together with 19% yield of the debromo compound. The observed low enantioselectivity will be attributed to the presence of the easily enolizable benzylic proton in the cyclization product.[10]

In summary, utilization of the Pd-catalyzed intramolecular coupling of aryl halides and amide-enolates in the formation of δ-lactam, leading to the synthesis of 4-arylisoquinoline alkaloids, has been reported. Further application of this methodology to the synthesis of other types of isoquinoline alkaloids is now under investigation in this laboratory.

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

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