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Construction of Erythrinane Skeleton via Pd(0)-Catalyzed Intramolecular Dearomatization of *para*-Aminophenols

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Supporting Information

ABSTRACT: A novel Pd(0)-catalyzed intramolecular arylative dearomatization of *para*-aminophenol derivatives is described. In the presence of 1.25 mol % $[Pd(C_3H_5)Cl]_2$ and 3.75 mol % RuPhos, the arylative dearomatization reaction proceeds smoothly for a broad range of substrates, offering an efficient synthetic route to erythrinane derivatives in excellent yields.

The erythrina alkaloids[1] as exemplified in Figure 1 display curare-like and hypnotic activity, and many compounds

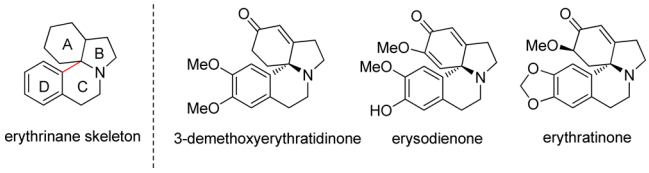

Figure 1. Natural erythrina alkaloids.

containing the erythrinane skeleton possess interesting biological activities including sedative, hypotensive, neuromuscular blocking, and CNS activity. Structurally, the most significant feature of the erythrina alkaloids is their unique tetracyclic spiroamine framework. This distinctive molecular structure along with biologically interesting activities of erythrina alkaloids has stimulated enormous synthetic investigations. Various approaches to access the core spirocyclic system of these alkaloids have been developed,[2,3] and most of them are based on the intramolecular cyclization of the quaternary-centered iminium ion, which generally requires multistep synthesis.[3] Nevertheless, highly efficient construction of erythrinane skeleton allowing structurally diverse modification remains in great demand.

Phenol and derivatives are readily available and serve as very important starting materials in organic synthesis. Transition-metal catalyzed dearomatization of phenol and derivatives[4] could produce highly reactive intermediates, leading to facile construction of cyclic compounds. Recently, pioneering studies on Pd-catalyzed cross-coupling type dearomatization of anilines, phenols, and indoles have been carried out by Buchwald and Bedford,[5] respectively. In 2011, Buchwald and co-workers reported an elegant palladium-catalyzed intramolecular arylative dearomatization of phenols to deliver spirocyclohexadienones in good to excellent yields.[5d] With our continuing interest in developing catalytic dearomatization reactions,[6] we envision that C ring in the erythrina alkaloids can be constructed through intramolecular dearomatization of 5-hydroxyl indoline by Pd-catalyzed cross-coupling type reaction, which will provide direct access to erythrinane skeleton. Despite the bulkiness of the nucleophile and energetic barrier encountered during the dearomatization process, the dearomative arylation reaction proceeded very well. Herein, we report such an efficient synthesis of this unique tetracyclic spiroamine framework via Pd(0)-catalyzed intramolecular dearomative arylation. The new methodology was found to be general for a wide range of substrates and applied in the total synthesis of erythrina alkaloids.

We began our investigation by testing 5-hydroxyl indoline derivative **1aa** with readily available palladium precursors and ligands. The results are summarized in Table 1. With $[Pd(C_3H_5)Cl]_2$ (2.5 mol %) and Ph_3P (7.5 mol %), the optimal catalyst in the dearomative arylation of indole derivatives,[6b] the reaction in the presence of K_2CO_3 (1.5 equiv) in toluene at 80 °C did not afford any arylative dearomatization product (Table 1, entry 1). Next, various phosphine ligands were systematically examined. To our great delight, we found that the desired dearomatized product (**2a**) was obtained in 36% yield when XPhos was utilized (Table 1, entry 2). The structure of product **2a** was further confirmed by an X-ray crystallographic analysis. After further investigating other commercially available phosphine ligands together with palladium precursors, we found that the combination of RuPhos (**L5**) with $[Pd(C_3H_5)Cl]_2$ delivered **2a** in 64% yield (Table 1, entry 6). By increasing the reaction temperature to 120 °C, the yield of **2a** could be further improved to 86% (Table 1, entry 12). The catalyst loading could be reduced to 1.25 mol % without decreasing the yield (90%, Table 1, entry 13). Further screening other reaction parameters including bases, solvents, and substrate concentrations did not improve the result (see the Supporting Information for details). Thus, the optimized conditions were obtained as the following: 1.25 mol % $[Pd(C_3H_5)Cl]_2$, 3.75 mol % RuPhos (**L5**), and 1.5 equiv of K_2CO_3 in toluene at 120 °C (Table 1, entry 13).

Under the above optimized reaction conditions, we then examined the scope of this reaction. The results are summarized in Table 2. Different halogen containing substrates (**1aa**−**1ac**) all gave their desired products in excellent yields (X = Cl, 85%; X = Br, 90%; X = I, 90%). Next, a wide range of substituted aryl bromides bearing both electron-donating and electron-withdrawing groups has been tested. In all cases, the intramolecular dearomatization reaction proceeded smoothly to afford their corresponding arylative products in moderate to excellent yields

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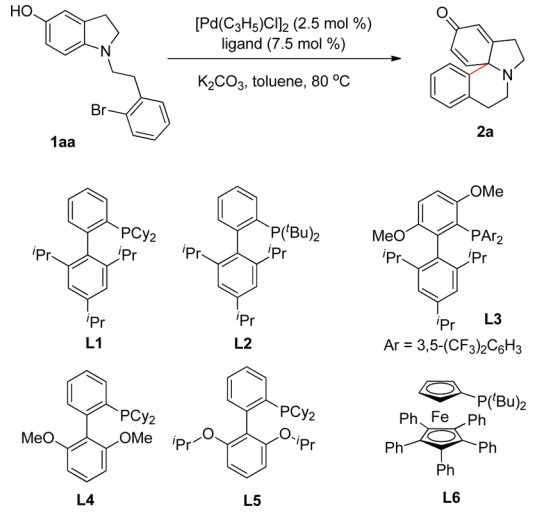
Table 1. Optimization of the Reaction Conditions[a]

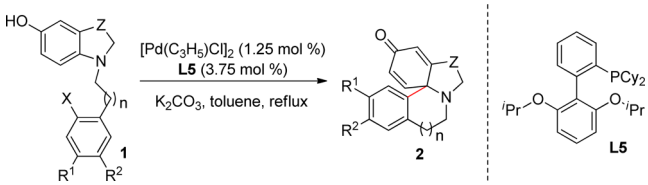


entry	[Pd]	ligand	yield (%)[b]
1	$[Pd(C_3H_5)Cl]_2$	Ph_3P	0
2	$[Pd(C_3H_5)Cl]_2$	**L1**	44/36[c]
3	$[Pd(C_3H_5)Cl]_2$	**L2**	15
4	$[Pd(C_3H_5)Cl]_2$	**L3**	11
5	$[Pd(C_3H_5)Cl]_2$	**L4**	61
6	*$[Pd(C_3H_5)Cl]_2$*	***L5***	*74/64*[c]
7	$[Pd(C_3H_5)Cl]_2$	**L6**	19
8	$Pd_2(dba)_3$	**L5**	64
9	$Pd(MeCN)_2Cl_2$	**L5**	65
10	$Pd(COD)Cl_2$	**L5**	61
11	$Pd(OAc)_2$	**L5**	18
12[d]	$[Pd(C_3H_5)Cl]_2$	**L5**	86[c]
13[e]	***$[Pd(C_3H_5)Cl]_2$***	***L5***	***90***[c]

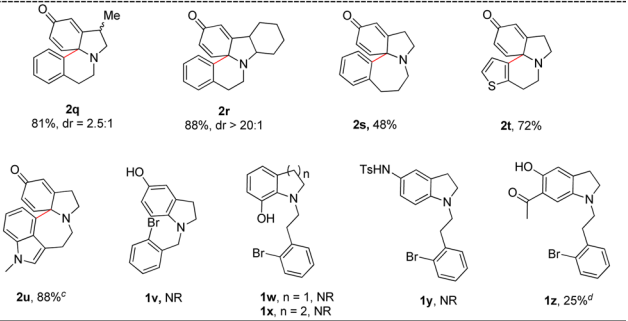
[a]Reaction conditions: **1aa** (0.2 mmol), $[Pd(C_3H_5)Cl]_2$ (0.005 mmol), ligand (0.015 mmol), K_2CO_3 (0.3 mmol) in toluene (1.0 mL), 80 °C, 8 h. [b]Determined by ^1H NMR using CH_2Br_2 (0.2 mmol) as internal standard. [c]Isolated yield. [d]Temperature 120 °C. [e]Reaction conditions: 1.25 mol % $[Pd(C_3H_5)Cl]_2$ and 3.75 mol % **L5** was used at 120 °C.

(68−92% yield, entries 4−10). Interestingly, the reaction of Cl substituted substrate **1b** underwent well to give product **2b** in 68% yield, where the Cl substituent survived. It is worth noting that the substrates possessing tetrahydroquinoline and benzo-[b][1,4]oxazine scaffolds were also found to be well tolerated. The desired products were obtained generally in excellent yields under the same reaction conditions (89−99% yield, entries 11−18). In addition, compounds **1q** and **1r** bearing additional substituents on the B ring were found also suitable substrates, affording the arylative products **2q** and **2r** in good yields (**2q**, 81% yield, dr = 2.5:1; **2r**, 88% yield, dr > 20:1). The size of C ring formed has great influence on this reaction. The desired product with a 7-membered ring was obtained in only 48% yield, and the reaction of substrate with one less carbon tether (**1v**) was sluggish. In addition, the substrates bearing a hydroxyl group *ortho* to the amine group (**1w** and **1x**) or aniline derivative (**1y**) were unreactive. The substrates possessing 3-bromo thiophene and 4-bromo indole were feasible in our standard conditions, giving the arylative products **2t** and **2u** in 72% and 88% yield, respectively. When substrate **1z** bearing an acyl substituent was employed, no dearomatization product was obtained. Interestingly, a 10-membered ring ketone α-arylation product was isolated in 25% yield (see the Supporting Information for details).

Table 2. Pd(0)-Catalyzed Intramolecular Arylative Coupling of 5-Hydroxyl Indolines[a]



entry	**1**: (R^1, R^2, X)	**2**, yield (%)[b]
1	**1aa**: X = Br	**2a**, 90
2	**1ab**: X = Cl	**2a**, 85
3	**1ac**: X = I	**2a**, 90
4	**1b**: R^1 = Cl, R^2 = H	**2b**, 68[c]
5	**1c**: R^1 = H, R^2 = F	**2c**, 92
6	**1d**: R^1 = H, R^2 = CF_3	**2d**, 78
7	**1e**: R^1 = Me, R^2 = H	**2e**, 91
8	**1f**: R^1 = H, R^2 = OMe	**2f**, 70
9	**1g**: R^1 = R^2 = OMe	**2g**, 90
10	**1h**: R^1, R^2 = -(CH_2OCH_2)-	**2h**, 84
11	**1i**: R^1 = H, R^2 = H	**2i**, 97
12	**1j**: R^1 = H, R^2 = F	**2j**, 89
13	**1k**: R^1 = Me, R^2 = H	**2k**, 92
14	**1l**: R^1 = R^2 = OMe	**2l**, 89
15	**1m**: R^1 = H, R^2 = H	**2m**, 99
16	**1n**: R^1 = H, R^2 = F	**2n**, 94
17	**1o**: R^1 = Me, R^2 = H	**2o**, 97
18	**1p**: R^1 = R^2 = OMe	**2p**, 99



[a]Reaction conditions: **1** (0.4 mmol), $[Pd(C_3H_5)Cl]_2$ (0.005 mmol), **L5** (0.015 mmol), K_2CO_3 (0.6 mmol) in toluene (2.0 mL), 120 °C. [b]Isolated yield. [c]**1** (0.2 mmol), $[Pd(C_3H_5)Cl]_2$ (0.0025 mmol), **L5** (0.0075 mmol), K_2CO_3 (0.3 mmol) in toluene (1.0 mL), 120 °C. [d]Ketone α-arylation product was isolated.

The asymmetric dearomatization of 5-hydroxyl indoline was also investigated. Screening of several commercially available

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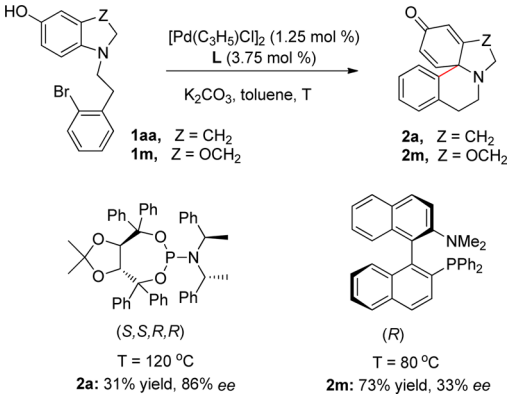
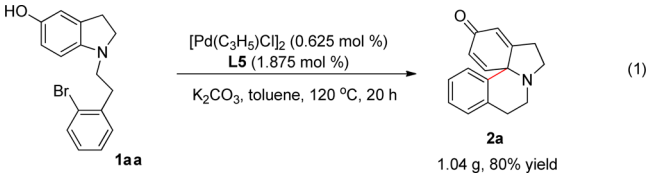
chiral phosphine ligands disclosed that in the presence of a TADDOL-derived phosphoramidite ligand, the promising enantioselectivity was obtained for substrate **1aa** albeit in moderate yield (31% yield, 86% *ee*). The best results for substrate **1m** were 73% yield and 33% *ee* (Scheme 1, see the Supporting Information for details).

Scheme 1. Preliminary Asymmetric Studies



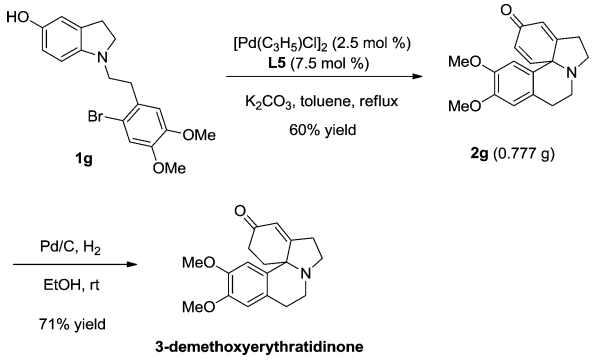
To test the practicality of the new methodology, a gram-scale reaction has been carried out. The intramolecular arylation of **1aa** in a 5.5 mmol scale gave the desired product in 80% yield, while the catalyst loading could be further reduced to 0.625 mol % (eq 1). Moreover, an efficient synthesis of erythrina alkaloid (3-



(1)

demethoxyerythratidinone) was developed. As shown in Scheme 2, the intramolecular dearomative arylation of **1g** in a 4.5 mmol

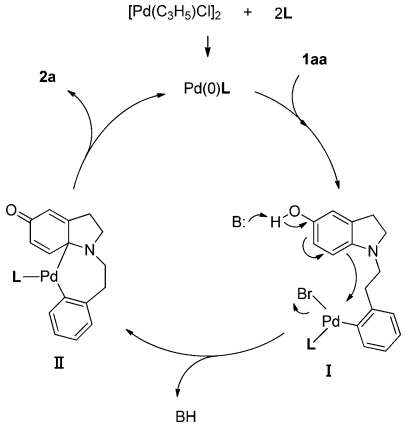
Scheme 2. Synthesis of 3-Demethoxyerythratidinone



scale gave the desired product (**2g**) with a slightly decreased yield (60%). Hydrogenation of **2g** mediated by Pd/C afforded 3-demethoxyerythratidinone in 71% yield under 1 atm H_2 at room temperature.[7]

A catalytic cycle was proposed as depicted in Scheme 3. The in situ formed Pd(0) undergoes oxidative addition with C–Br bond in **1aa** affording intermediate I. Assisted by base, the *para*-aminophenol moiety proceeds ligand exchange to form

Scheme 3. Proposed Catalytic Cycle



intermediate II, which then undergoes reductive elimination to afford product **2a** and finishes the catalytic cycle.

In summary, we have developed a highly efficient intramolecular dearomative arylation of 5-hydroxyl indoline to afford tetracyclic sterically congested spiroamines in excellent yields. The dearomatized products could be readily transformed to erythrina alkaloids such as 3-demethoxyerythratidinone. The reaction conditions are also compatible for phenol derivatives of tetrahydroquinoline and 3,4-dihydro-2*H*-benzo[b][1,4]oxazine. The preliminary studies reveal that the asymmetric dearomatization is also feasible. Synthesis of more complex erythrina alkaloids and development of more efficient catalytic asymmetric systems are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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