# A four-step synthesis of (±)-γ-lycorane via $Pd^0$-catalyzed double C($sp^2$)–H/C($sp^3$)–H arylation

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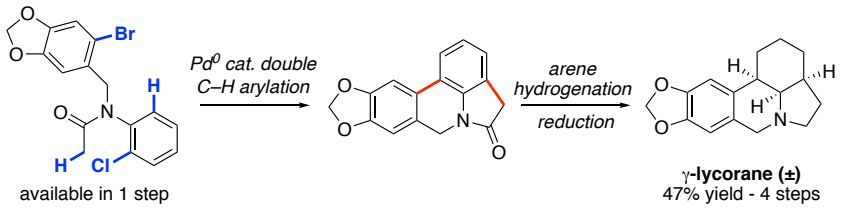
*Supporting Information Placeholder*




**ABSTRACT:** An expedient synthesis of lycorine alkaloids is reported using a palladium(0)-catalyzed double C–X/C–H arylation as key step. The selectivity of this reaction was controlled through a judicious choice of the two halogen atoms, and its generality was demonstrated through the construction of various substituted pyrrolophenanthridinones. A selective arene hydrogenation allowed for the completion of the synthesis of (±)-γ-lycorane in just four steps from commercially available precursors.

Lycorines constitute an abundant subclass of fused polycyclic *Amaryllidaceae* alkaloids which possess diverse interesting biological properties[1] and have been the subject of numerous synthetic studies.[2] As shown with the structure of hippadine (**1a**), pratosine (**1b**), assoanine (**2**), lycorine (**4**) and its degradation product γ-lycorane (**3**),[3] the B, C and D rings of lycorines occur in diverse oxidation states (Figure 1).

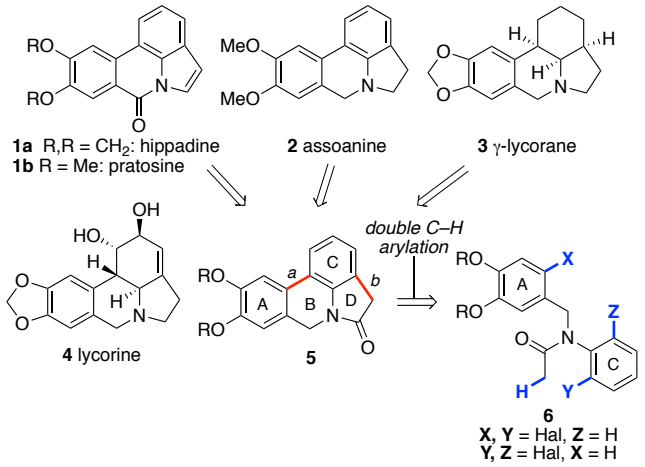



**Figure 1** Examples of lycorine alkaloids and retrosynthetic analysis.

As a consequence, fused biaryls **5** would constitute appealing retrons allowing access to a variety of lycorine congeners in a divergent fashion.[4] Based on our previous work,[5] we envisioned to disconnect compounds **5** simultaneously at bonds *a* and *b* by means of a $Pd^0$-catalyzed double C–X/C–H arylation,[6,7] hence leading to bis-halogenated precursors **6**, wherein the halogen atoms are located either on rings A and C or both on ring C. The corresponding individual C($sp^2$)–X/C($sp^2$)–H and C($sp^2$)–X/C($sp^3$)–H arylations are known,[8,9] but to the best of our knowledge they have not been combined in a domino process. However, two main issues were expected to arise from this strategy: 1. the generation of the strained B-C-D ring system, potentially affecting the efficiency of the second C–H arylation step; 2. the site-selectivity of the C–H activation steps, potentially leading to isomeric mixtures. These issues notwithstanding, compounds **6** would be readily accessible from commercially available aniline and benzyl bromide precursors, thereby providing a straightforward and scalable access to lycorines. Herein, we report the development of this domino C–H arylation strategy and its application to the short and efficient synthesis of lycorine alkaloids.

At the onset of this work, we looked for the most appropriate bis-halogenated precursor to obtain compound **5a** selectively and efficiently (Scheme 1, Table 1). The double C–X/C–H arylation was first conducted with compound **6a** bearing the two bromine atoms on the same ring. Tricyclohexylphosphine was chosen as ligand, because it was previously employed in both individual C($sp^2$)–H[8d] and C($sp^3$)–H[9b] arylations. The well-defined $Pd(PCy_3)_2$ complex, which was found to provide superior yields to *in situ* generated catalysts in previous strain-generating C($sp^3$)–H activation reactions,[10] was employed as the catalyst, and cat. $PivOK/K_2CO_3$ as the basic system.[11] Under these conditions, the double C–Br/C–H arylation took place, but isomer **5b**, arising from the electronically-favored activation of the C($sp^2$)–$H_b$ bond (**A** → **B**) instead of the more sterically accessible C($sp^2$)–$H_a$ bond (Scheme 1 top), was isolated as the sole C–H arylation product, consistent with initial observations from Harayama and co-workers (entry 1).[12] To solve this site-selectivity issue, we examined the reaction of isomeric dibromide **6b**, bearing bromine atoms on rings A and C (entry 2, Scheme 1 bottom).

**Scheme 1 Mechanistic and Selectivity Considerations for the Double C–X/C–H Arylation**

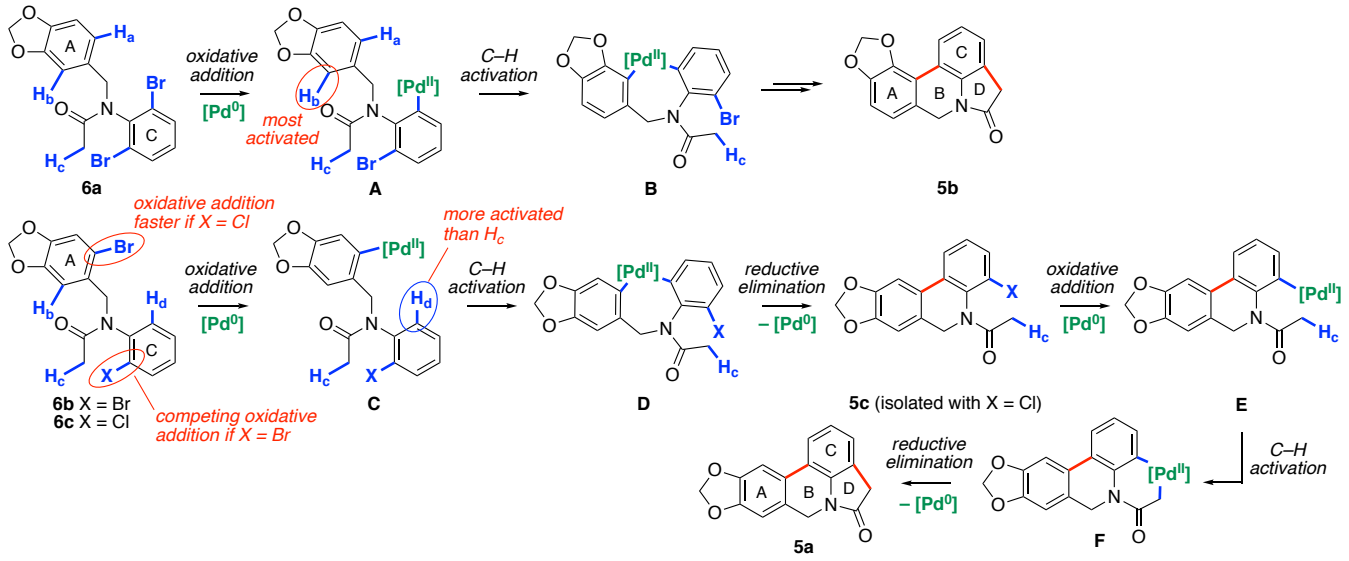



**Table 1. Optimization of Substrate and Reaction Conditions**

| entry | reactant | conditions | product | yield (%) |
|---|---|---|---|---|
| 1 | **6a** | $Pd(PCy_3)_2$ (10 mol %), PivOK (30 mol %), $K_2CO_3$ (4 equiv), mesitylene, 140 °C, 16 h | **5b** | 60[a] |
| 2 | **6b** | same as above | **5a** | 22[b] |
| 3 | **6c** | same as above | **5a** | 37[b] |
| 4 | **6c** | $Pd(OAc)_2$ (10 mol %), $PCy_3$ (20 mol %), PivOH (30 mol %), $Cs_2CO_3$ (2 equiv), mesitylene, 140 °C, 16 h | **5a** | 53[b] |
| 5 | **6c** | $Pd(PCy_3)_2$ (10 mol %), PivOH (30 mol %), $Cs_2CO_3$ (2 equiv), mesitylene, 140 °C, 16 h | **5a** | 90[b] (92)[a] |

[a]Yield of the isolated product. [b]NMR yield using trichloroethylene as internal standard.

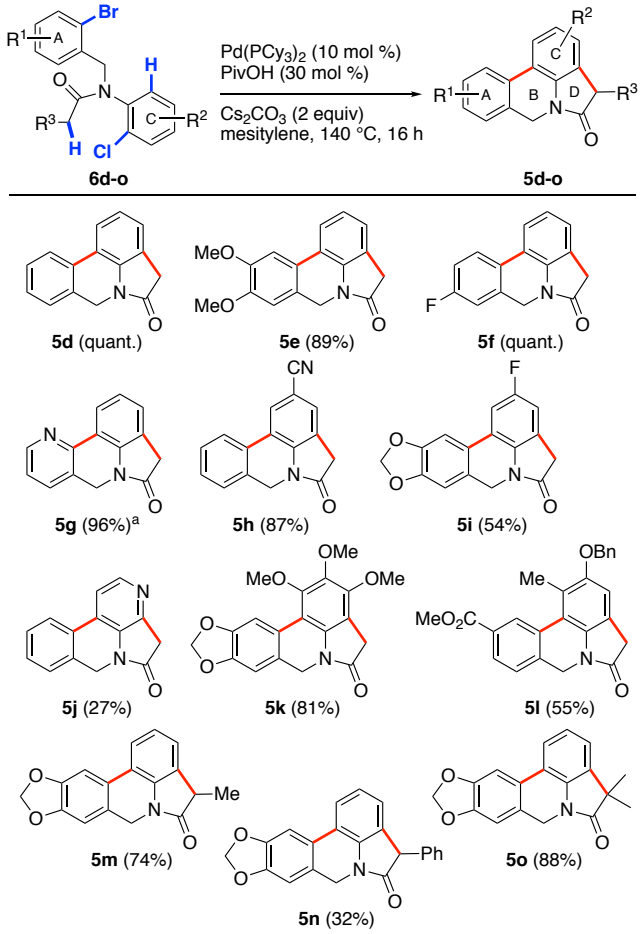
Under the same conditions, the desired product **5a** was isolated, albeit in low yield and with byproducts arising from competitive arylation at C–$H_b$ and proto-debromination. A simple solution was found by replacing the bromine atom on ring C with a chlorine atom (**6c**). Indeed, in this case the oxidative addition of the C–Br bond to $Pd^0$ should occur faster than that of the C–Cl bond, to give intermediate **C**. Upon activation of the most reactive C($sp^2$)–$H_d$ bond *vs.* the less reactive C($sp^3$)–$H_c$ bonds, ring B would be formed with the correct regiochemistry via palladacycle **D**. Then C–Cl oxidative addition, enabled by the electron-rich $PCy_3$ ligand, would furnish complex **E**, followed by activation of a C–$H_c$ bond to give palladacycle **F**, which would allow for the construction of ring D upon reductive elimination. Accordingly, compound **6c** furnished the desired product **5a** in higher yield (37%), and importantly by-products arising from competitive C–$H_b$ or C–$H_c$ arylations were not detected (entry 3). Gratifyingly, tuning the reaction conditions (see the Supporting Information for details), and in particular replacing potassium with cesium carbonate (2 equiv), allowed isolation of product **5a** in excellent (92%) yield (entry 5). Although in situ catalyst generation such as $Pd(OAc)_2/PCy_3$ could be also employed (entry 4), it provided a markedly lower yield than the well-defined $Pd(PCy_3)_2$ complex. When the reaction was stopped at incomplete conversion (15 min), the monocyclized product **5c**, arising from C($sp^2$)–Br/C($sp^2$)–H arylation, was isolated in 68% yield along with **5a**, thereby validating the hypothesized order of events.

Next, we studied the scope of the double C–X/C–H arylation (Scheme 2). We were pleased to find that a variety of substituents possessing different electronic properties were well tolerated on rings A and C (**5d-l**). As shown above, the regioselectivity control should be good as far as the oxidative addition to $Pd^0$ occurs first on ring A. Hence, problems were expected to arise upon increase of the electron density on ring A and decrease on ring C, i. e. for substituents slowing down the oxidative addition on the former and accelerating it on the latter. This seemed to be the case for compounds **5i-j**, for which a lower yield was indeed obtained, although we were unable to clearly identify isomeric products in the reaction mixture. In all other cases good to excellent yields of the desired polycyclic products were obtained. Substituents in α position to the amide ($R^3$) were also well tolerated (**5m-o**), consistent with previous results on the individual C($sp^3$)–H arylation reaction,[9] despite the fact that a weaker base was employed in the current work (PivOK, *vs. t*-BuOK or LiHMDS in previous work).

The application of this method to the synthesis of lycorine alkaloids is depicted in Scheme 3. The C–H arylation precursor **6c** was obtained in one step from commercially available substrates **7-8**. The double C–H arylation described in Table 1 was scaled up to give 1.4 g of pyrrolophenanthridinone **5a** (81% yield). Then, we considered directly converting **5a** to γ-lycorane **3** through selective arene hydrogenation. We recognized that achieving selectivity for ring C over ring A might be particularly challenging because, as shown with the calculated HOMO of **5a** (Figure 2, left), both aromatic rings bear similar electron density and should therefore react at comparable rates.[13] However, ring C is also more strained than ring A thanks to the adjacent ring fusions with rings B and D, as shown with the more distorted bond angles in ring C (Figure 2,

right). As a consequence, ring C might undergo selective hydrogenation by virtue of strain release.[14] Such a selective arene hydrogenation is rare, but was already reported on the reduced form of **5a** – i.e. amine instead of amide – in the context of γ-lycorane semi-synthesis using $PtO_2$ as the catalyst in AcOH,[3] albeit only with low yields (8-24%).

**Scheme 2. Scope and Limitations of the Double C–X/C–H Arylation**




[a]From the dichloride precursor.

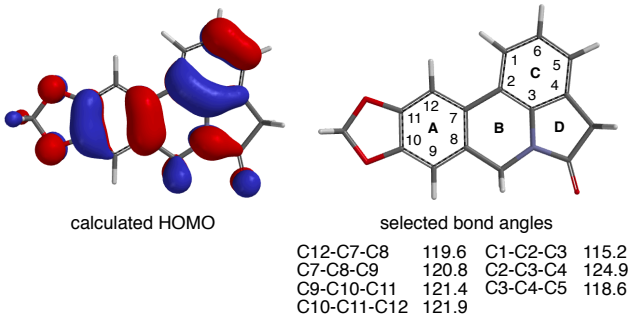
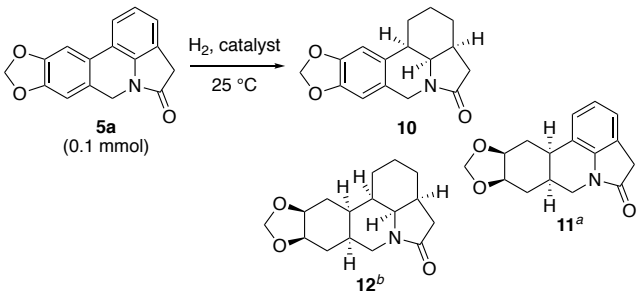


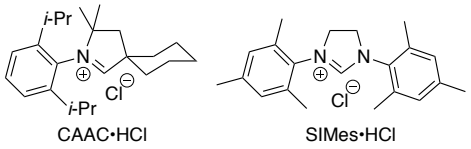

**Figure 2.** DFT-optimized structure of **5a** (ωB97X-D/6-31G**) showing the HOMO (left) and selected bond angles (right).

We examined various heterogeneous and homogeneous catalysts and reaction conditions, and selected representative examples are displayed in Table 2. Whereas $PtO_2$ in AcOH was found to be inactive (entry 1), Pd/C in HFIP under forcing conditions provided **10** as the major product (entries 2-3), but together with compound **11** arising from the competitive hydrogenation of ring A. Of note, both hydrogenated products **10-11** were obtained as *cis*,*cis* diastereoisomers (d.r. >95:5). Gratifyingly, turning to the more active Rh/C catalyst under milder conditions (room temperature, 6 bar $H_2$) allowed suppression of the undesired isomer **11** (entry 4).[15] At a higher hydrogen pressure, the completely hydrogenated product **12** was mainly formed (entry 5). We also examined various homogeneous catalysts and in particular Rh-carbene complexes as reported by Zeng and co-workers.[16] Similar results to Rh/C were obtained using two different carbene precursors, but at a higher pressure (entries 6-7).[17]

**Table 2. Selective Hydrogenation of Pyrrolophenanthridinone 5a**




| entry | catalyst | solvent[c] | P($H_2$) (bar) | product(s) (% yield)[d] |
|---|---|---|---|---|
| 1 | $PtO_2$ (10 mol %) | AcOH | 50 | – |
| 2[e] | Pd/C (10 mol %) | HFIP | 50 | **10** (41), **11** (5) |
| 3[e] | Pd/C (20 mol %) | HFIP | 50 | **10** (55), **11** (17) |
| 4 | Rh/C (30 mol %) | HFIP | 6 | **10** (66) (62)[f] |
| 5 | Rh/C (30 mol %) | HFIP | 10 | **10** (30), **12** (60) |
| 6 | [Rh(COD)Cl]$_2$/ CAAC•HCl/ *t*-BuOK (20 mol %) | TFE | 50 | **10** (64) |
| 7 | [Rh(COD)Cl]$_2$/ SIMes•HCl/ *t*-BuOK (20 mol %) | TFE | 50 | **10** (73) |

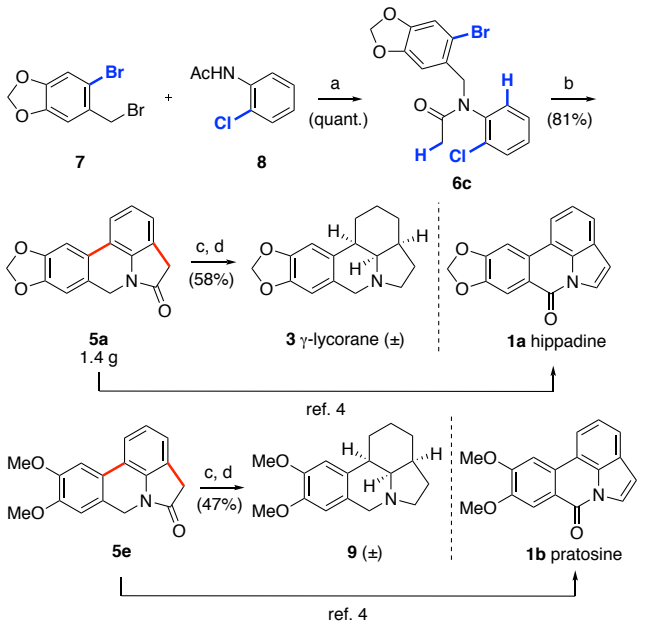



[a]Relative configuration determined by NOESY. [b]Presumed major diastereoisomer based on the configuration of **10** and **11**. [c]$c$ = 0.06 M, $V$ = 1.8 mL. [d]NMR yield using trichloroethylene as internal standard. [e]Performed at 50 °C instead of 25 °C. [f]Yield of the isolated product. HFIP = hexafluoroisopropanol, TFE = 2,2,2-trifluoroethanol.

The hydrogenation of **5a** was then repeated using Rh/C as the catalyst and 6 bar $H_2$ pressure on a 0.5 mmol scale, to give γ-lycorane in 58% yield for two steps after amide reduction with $LiAlH_4$ (Scheme 3). Overall, (±)-γ-lycorane was obtained in only four steps, 47% overall yield, from commercially available precursors **7-8**, which to the best of our knowledge is the shortest and highest-yielding synthesis to date.[18] In addition to

**5a**, dimethoxy-substituted compound **5e** was converted to γ-lycorane analogue **9** through the same reductive sequence. Moreover, pyrrolophenanthridinones **5a** and **5e** are valuable platforms for the synthesis of more oxidized lycorine alkaloids such as hippadine **1a** and pratosine **1b**, which were synthesized as previously reported.[4]

**Scheme 3. Synthesis of Lycorine Alkaloids**[a]




[a]Reagents and conditions: a) **8** (1 equiv), NaH, then **7** (1.1 equiv), THF, reflux; b) $Pd(PCy_3)_2$ (10 mol %), PivOH (30 mol %), $Cs_2CO_3$ (2 equiv), mesitylene, 140 °C; c) $H_2$ (6 bar), Rh/C, HFIP, 25 °C; d) $LiAlH_4$, THF, reflux.

In conclusion, an expedient synthesis of lycorine alkaloids was achieved using a palladium(0)-catalyzed double C–X/C–H arylation, the selectivity of which being controlled through a judicious choice of the two halogen atoms. The generality of this reaction was demonstrated through the construction of various substituted pyrrolophenanthridinones. A selective arene hydrogenation allowed for the completion of the synthesis of (±)-γ-lycorane in just four steps from commercially available precursors.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at
Full optimization tables, procedural and spectral data, computational details.

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### Notes

The authors declare no competing financial interest.

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(17) Of note, we failed to achieve enantioselective hydrogenation using chiral carbenes.

(18) The previous shortest synthesis of (±)-γ-lycorane includes 6-7 steps, 30.6% overall yield.[3e]