A Concise Total Synthesis of (±)-Stepharine and (±)-Pronuciferine

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Abstract We herein report a concise total synthesis of (±)-stepharine and (±)-pronuciferine using readily available reagents as the starting materials. This synthesis features a three-component Catellani reaction/Au-catalyzed *6-exo-dig* cyclization for the assembly of 1-methylene-THIQ scaffold and an oxidative dearomatization for constructing spiro-cyclohexadienone scaffold.

Stepharine (**1**) and pronuciferine (**2**) (Figure 1A) are two representative members of proaporphine alkaloids, which are also biosynthetic precursors to biologically important aporphine alkaloids.[1] They were reported to display important biological activities.[2-3] For instance, stepharine exhibits antihypertensive activity and can inhibit cholinesterase and pseudocholinesterase *in vitro*.[2] Pronuciferine has been applied for the treatment of medical ailments.[3]

The structure of **1** and **2** feature a 6-6-5-6 ring system, including a tetrahydroisoquinoline (THIQ) moiety and a spiro-cyclohexadienone skeleton. The interesting molecular architecture and promising biological activities render them intriguing targets for chemical synthesis. Several elegant total syntheses of stepharine and/or pronuciferine have been completed by Bernauer,[4] Iwata,[5] Honda,[6] Magnus[7] and others.[8] However, there is still room for improving the overall synthetic efficiency, in

particular, developing a more efficient method to assemble the core THIQ motif.

Recently, we reported an efficient three-component protocol for the construction of 1-methylene-THIQ scaffold,[9] which involved a Catellani reaction,[10] followed by a desilylation and a Au-catalyzed cyclization (Figure 1B).[11] Readily available aryl iodides, *N*-protected aziridines and (trialkylsily)acetylene were utilized as the reactants. As such, we envisioned that this new method might be applicable for a convergent synthesis of stepharine (**1**) and pronuciferine (**2**).

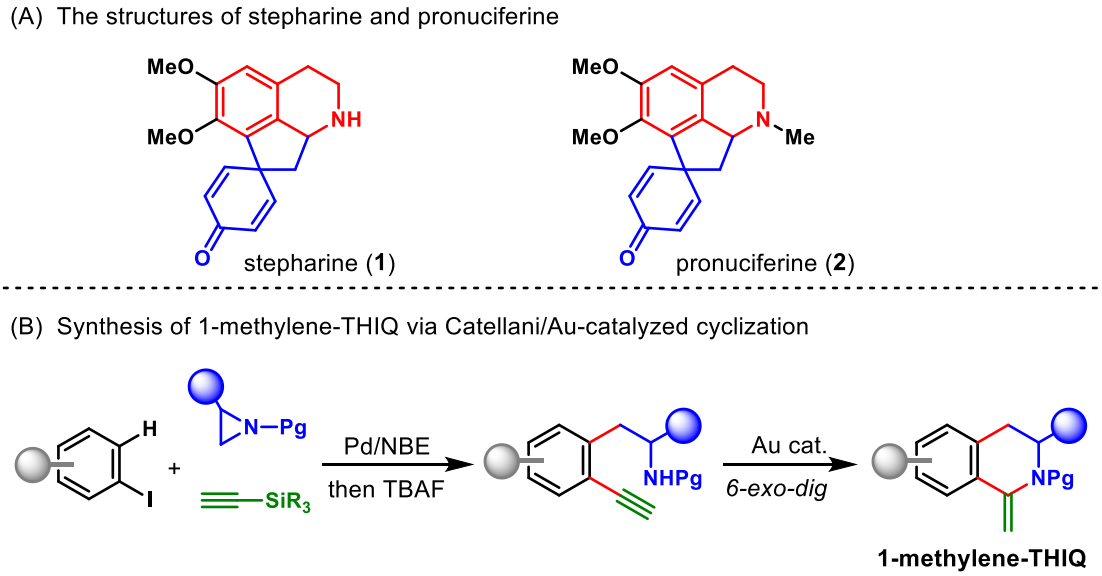
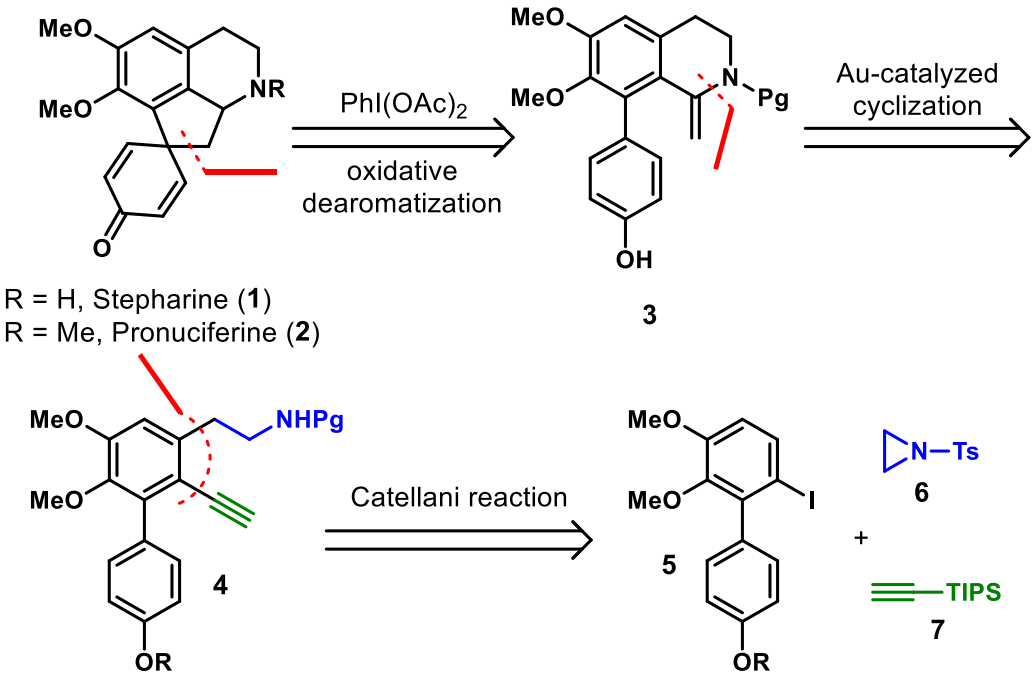


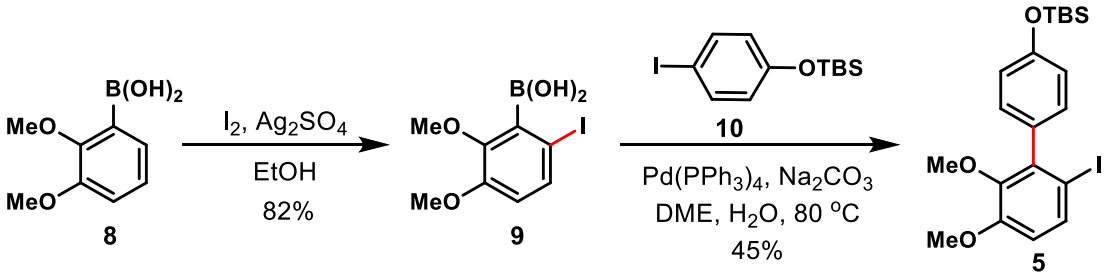
Figure 1. The structures of stepharine and pronuciferine and planned synthetic method for their syntheses.

A retrosynthetic analysis of stepharine (**1**) and pronuciferine (**2**) based on our new method is presented in Scheme 1. Firstly, the spiro-cyclohexadienone scaffold can be assembled from 1-methylene-THIQ **3** via an aromatic oxidation with a hypervalent iodine reagent followed by reduction, referring to Honda's work[6]. Then, **3** can be obtained through an Au-catalyzed *6-exo-dig* cyclization of 2′-alkynylaryl-2-ethylamine **4**. Lastly, the key intermediate **4** can be quickly synthesized from aryl iodide **5**, aziridine **6** and (triisopropylsily)acetylene **7** via a Catellani reaction.[9]



Scheme 1 Retrosynthetic analysis of stepharine (**1**) and pronuciferine (**2**).

We started our synthesis with the preparation of building block **5** to investigate the key three-component Catellani reaction. As shown in Scheme 2, aryl iodide **5** was prepared in two steps from commercially available (2,3-dimethoxyphenyl)boronic acid (**8**). Firstly, iodination of **8** with I_2 in the presence of Ag_2SO_4 gave iodide **9** in 82% yield. Subsequently, a Suzuki coupling reaction of boronic acid **9** with aryl iodide **10** provided **5** in 45% yield. In addition, aziridine **6**[12] and (triisopropylsily)acetylene **7** are widely used simple reagents.

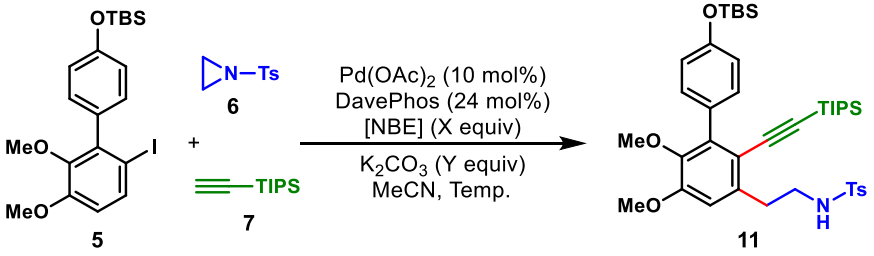


Scheme 2 Synthesis of building block **5**.

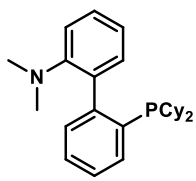
We then explored the key three-component Catellani reaction of **5**, **6** and **7** to access 2′-alkynylaryl-2-ethylamine **11** (Table 1). Firstly, **5**, **6** and **7** were subjected to our previously developed reaction conditions: 10 mol% of $Pd(OAc)_2$, 24 mol% of DavePhos, 50 mol% of **N**[1], 1.0 equivalents of K_2CO_3 in CH_3CN at 70 °C under Ar.[9] To

our delight, the desired product **11** was obtained in 29% yield, along with substantial amounts of the direct Sonogashira coupling side product **11′** by **5** and **7** (Table 1, entry 1). To our delight, the yield of product **11** was significantly improved to 43% by using 2.0 equvalents of 5-norbornene-2-carbonnitrile **N²** as the mediator (Table 1, entry 2). However, the extensive screening of other reaction parameters, including lowering the reaction temperature and reducing the amount of base, failed to further improve the reaction efficiency (Table 1, entries 3-4), which was mainly due to the unstablity of **5** under the basic reaction conditions. Thus, we concluded that 2-aryl substituted aryl iodide **5** was not be an ideal substrate for the key Catellani reaction.

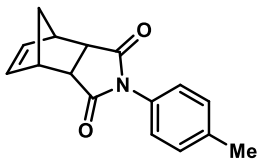
Table 1. Preliminary examination of the Catellani reaction to access 11



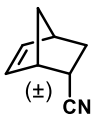
Entry[a]	[NBE]	X	Y	Temp.	Yield of **11** [%][b]
1	**N¹**	0.5	1.0	70 °C	29
2	**N²**	2.0	1.0	70 °C	43
3	**N¹**	0.5	0.5	60 °C	32
4	**N²**	2.0	0.5	60 °C	37



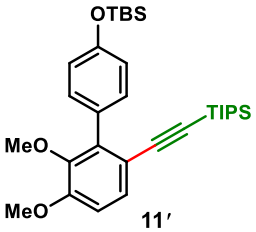
DavePhos



N¹



N²



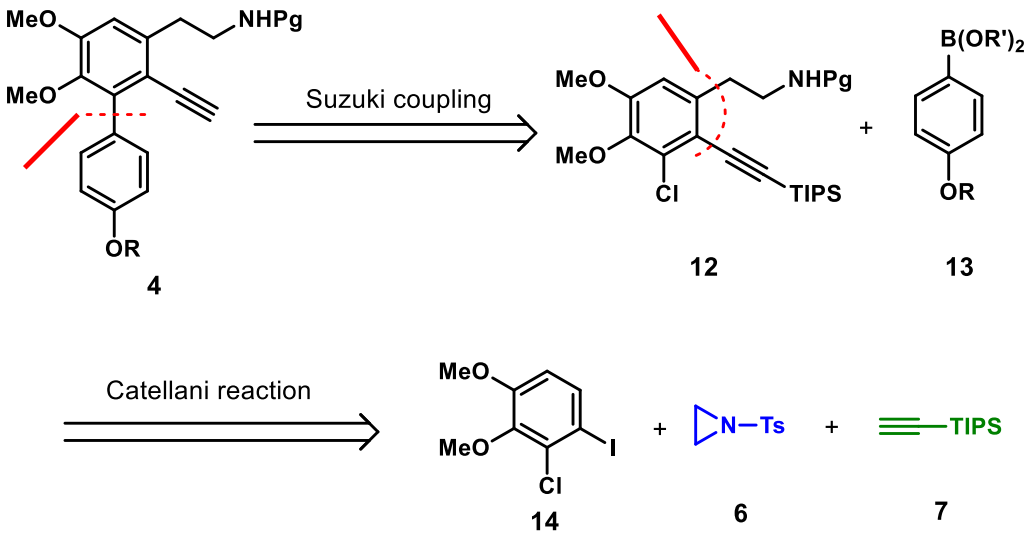
11′

[a] All reactions were performed on a 0.1 mmol scale.

[b] ^{1}H NMR yield with 1,3,5-trimethyoxybenzene as an internal standard.

We turned to modify the original synthetic plan. As shown in Scheme 3, we envisioned that intermediate **4** can be synthesized via a Pd-catalyzed Suzuki-Miyaura coupling reaction of aryl chloride **12** and boronic acid **13**.[13] **12** can be quickly constructed from simple building blocks aryl iodide **14**, aziridine **6** and

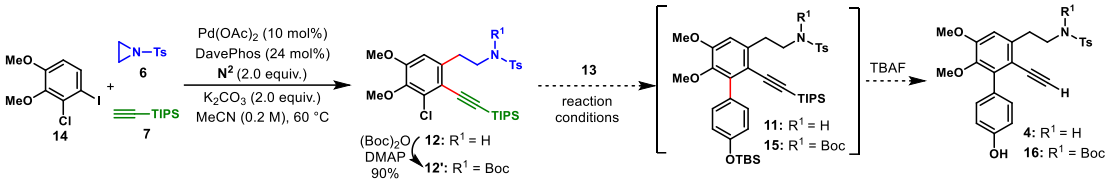
(triisopropylsily)acetylene **7** via Pd/NBE cooperative catalysis. **14** proved to be a robust substrate for Catellani-type reactions.[9,14]



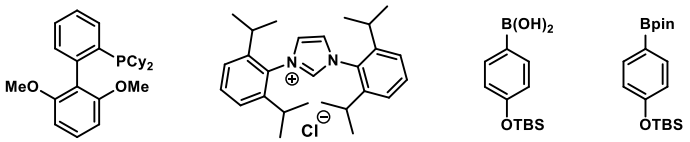
Scheme 3 Revised retrosynthetic analysis of intermediate **4**.

Indeed, under a similar reaction conditions of Table 1 (entry 2), 2′-alkynylaryl-2-ethylamine intermediate **12** was successfully assembled by **6**, **7** and **14** via Pd/NBE cooperative catalysis in a good yield (62%, 2.0 mmol scale) (see Table 2). Next, we investigated the Suzuki-Miyaura coupling reaction to install the aryl group. As shown in Table 2, we initially examined the reaction of aryl chloride **12** with boronic acid **13a** under Yajima's conditions ($Pd(OAc)_2$, SPhos and K_3PO_4 in toluene).[13c] However, only a trace amount of desired product (**11**) was observed (Table 2, entry 1). The reaction didn't work either by change of base (e.g., NaOH or Na_2CO_3 instead of K_3PO_4) (Table 2, entries 2-3) or under Organ's conditions (Pd_2dba_3·$CHCl_3$, IPr·HCl and Cs_2CO_3 in dioxane) (Table 2, entry 4). We surmised that these unfruitful results are probably due to the free N–H group of **12**, which may deactivate the palladium catalyst through a strong coordination interaction. Indeed, to our delight, the Suzuki-Miyaura coupling of **12′** (the Boc-protected analog of **12)** with **13a** proceeded smoothly under Yajima's conditions to provide the desired product **15**, which subsequently underwent an in situ desilylation to afford the terminal arylacetylene **16** in 72% yield (Table 2, entry 5). Notably, the yield of **16** was further improved to 77% by performing the Suzuki-Miyaura coupling reaction of **12′** with **13b** (the pinacol ester of **13a**) (Table 2, entry 6).

Table 2. Optimization of Suzuki-Miyaura coupling of aryl chloride 12 with boronic acid derivative 13



Entry[a]	**12**	**13**	Reaction conditions	Solvent	Temp. (°C)	Product	Yield (%)[b]
1	**12**	**13a**	$Pd(OAc)_2$ (10 mol%), SPhos (24 mol%), K_3PO_4 (2.0 equiv)	toluene	95-110	**11**	trace
2	**12**	**13a**	$Pd(OAc)_2$ (10 mol%), SPhos (24 mol%), NaOH or Na_2CO_3 (2.0 equiv)	toluene	95-110	**11**	trace
3	**12**	**13a**	$Pd(OAc)_2$ (10 mol%), SPhos (11 mol%), NaOH (10 equiv)	toluene	95-110	**11**	NR
4	**12**	**13a**	$Pd_2(dba)_3$·$CHCl_3$ (10 mol%), IPr·HCl (11 mol%), Cs_2CO_3 (2.0 equiv)	dioxane	80-110	**11**	NR
5	**12′**	**13a**	$Pd(OAc)_2$ (10 mol%), SPhos (24 mol%), NaOH (10 equiv)	toluene	95	**16**	72
6	**12′**	**13b**	$Pd(OAc)_2$ (10 mol%), SPhos (24 mol%), NaOH (10 equiv)	toluene	95	**16**	77



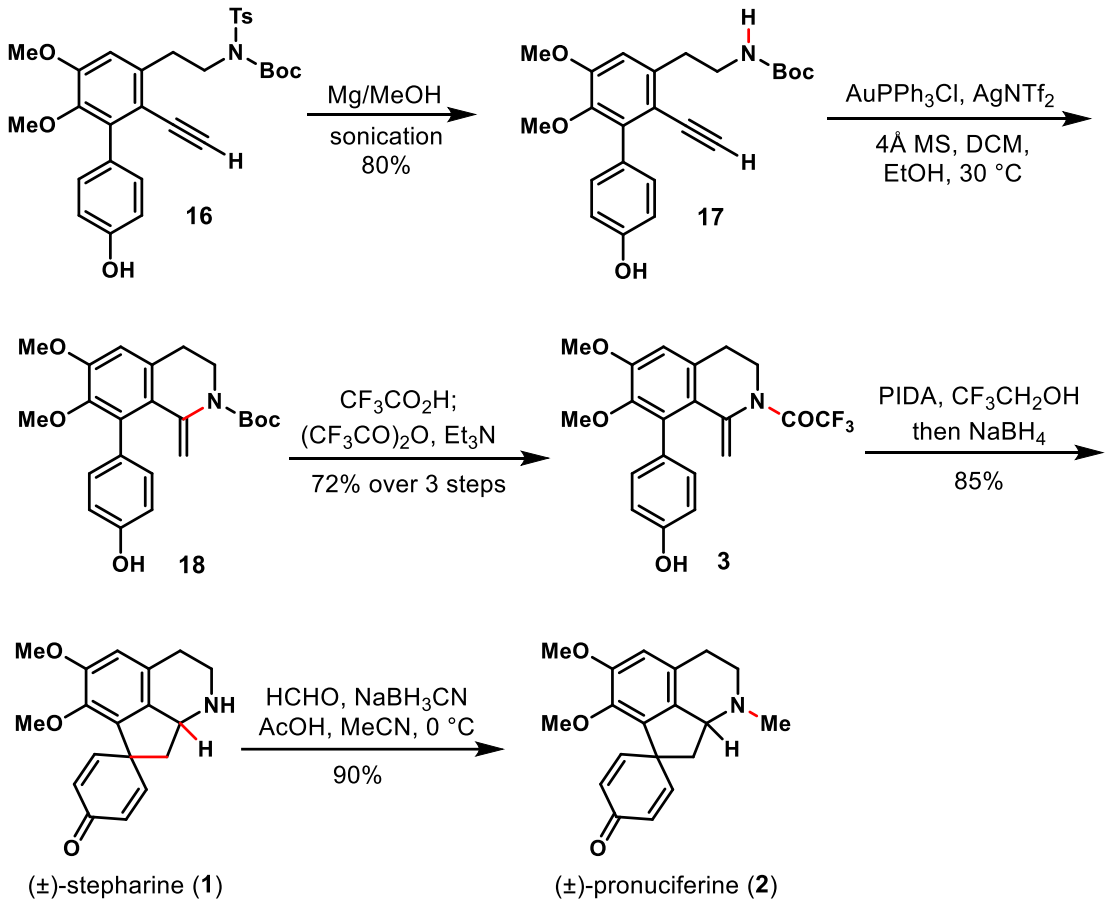
SPhos IPr·HCl **13a** **13b**

[a] All reactions were performed on a 0.1 mmol scale.

[b] Isolated yield.

With the key intermediate **16** in hand, we then focused on the construction of the 1-methylene-THIQ **3** (Scheme 4). First, the removal of *N*-tosyl group was realized by Mg/MeOH to give **17** in 80% yield. Then, **17** was subjected to a Au/Ag-catalyzed *6-exo-dig* cyclization to provide 1-methylene-THIQ **18** uneventfully. A following efficient 2-step protecting group manipulation led to the reported enamide **3** by Honda[6] (72% yield over three steps). Finally, stepharine (**1**) was obtained in 85% yield through the iodobenzene diacetate (PIDA)-promoted oxidative dearomatization of **3** followed by sodium borohydride reduction, according to the reported procedure.[6] An additional reductive amination of stepharine (**1**) furnished pronuciferine (**2**) in 90% yield. The

NMR spectra of both stepharine (**1**) and pronuciferine (**2**) are in good agreement with those previously reported[6] (see supporting information for the corresponding comparisons).



Scheme 4 Total synthesis of (±)-stepharine (**1**) and (±)-pronuciferine (**2**).

In summary, we have accomplished a concise total synthesis of (±)-stepharine in 7 steps with an overall yield of 21% and (±)-pronuciferine in 8 steps with an overall yield of 19% starting from readily available reagents. This synthesis features a three-component Catellani reaction/Au-catalyzed *6-exo-dig* cyclization for the assembly of 1-methylene-THIQ scaffold and an oxidative dearomatization for constructing spiro-cyclohexadienone scaffold. We expect this strategy will have broad application in the total synthesis of complex bioactive natural products.

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Competing interests The authors declare no competing interests.

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