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Ruthenium Catalyzed Tandem Pictet–Spengler Reaction

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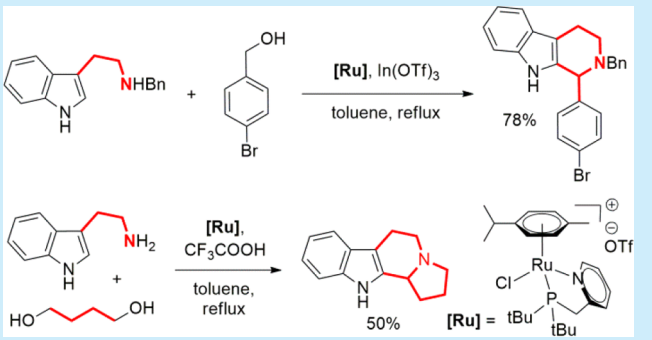
ABSTRACT: We report a pyridyl-phosphine ruthenium(II) catalyzed tandem alcohol amination/Pictet–Spengler reaction sequence to synthesize tetrahydro-β-carbolines from an alcohol and tryptamine. Our conditions use a Lewis acid cocatalyst, $In(OTf)_3$, that is compatible with typically *base catalyzed* amination and an *acid catalyzed* Pictet–Spengler cyclization. This method proceeds well with benzylic alcohols, heterocyclic carbinols, and aliphatic alcohols. We also show how combining this reaction with a subsequent cycloamination enables a direct synthesis of tetracyclic alkaloids like harmicine.



The indole alkaloids are one of the largest and most medicinally important classes of the alkaloid natural products.[1] Many feature a tetrahydro-β-carboline (THBC) core; for example, approved drugs in this group include the nonsteroidal anti-inflammatory drug etodolac,[2] tadalafil,[3] reserpine,[4] and strictosidine,[5] which is a synthetic gateway to ajmalicine,[6] serpentine,[7] and quinine[8] (Figure 1B). Among the many routes to tetrahydro-β-carboline derivatives,[9] the most widely used is the biomimetic Pictet–Spengler cyclization,[10,11] originally discovered by Ame Pictet and Theodor Spengler in 1911.[12] This reaction is employed in the synthesis of simple THBCs, and the requisite aldehydes are usually prepared from alcohols. Thus, development of a tandem reaction[13] for THBC formation directly from alcohols is a useful way to enable step savings in the construction of these scaffolds while obviating the isolation of a delicate intermediate aldehyde. Further, the realization of conditions for direct reactions of alcohols opens the way for a biomimetic cascade sequence in which additional rings are annulated onto the THBC core.

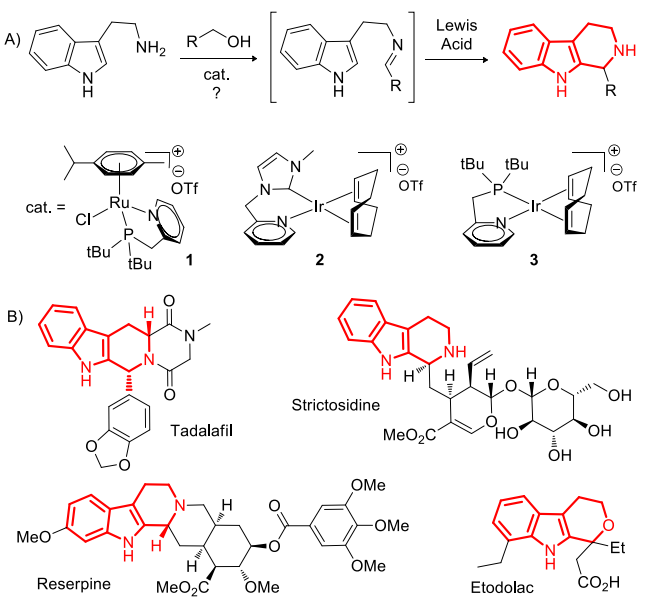


Figure 1. (A) Proposed synthesis of THBCs. (B) Examples of pharmaceutically relevant THBCs.

Hydrogen borrowing catalysis[14] enables a green, waste-free, and cost-efficient approach for alcohol amination.[15] Several ruthenium[16] and iridium[17] complexes highlight the many examples of this scheme. We have long considered the development of a tandem hydrogen borrowing amination followed by a Pictet–Spengler reaction (PSR) step (Figure 1A), because this is conceptually the same route through which nature assembles the indole alkaloids.[1] Such a strategy has an intrinsic problem: Pictet–Spengler cyclization is enabled by the electrophilicity of an intermediate imine, which necessitates a Bronsted or Lewis[18] acid catalyst,[19,11f] whereas most hydrogen borrowing catalysts rely on a strong base to activate an alcohol for β-hydride elimination.[17h–k] This adds a challenge to the tandem PSR problem that is not present in the recent tandem aldol–cyclization work.[20] Resolving this dilemma, our group introduced a base-free (pyridyl)phosphine ruthenium(II) catalyst, [RuCl(η^6-cymene){(2-pyridyl)-

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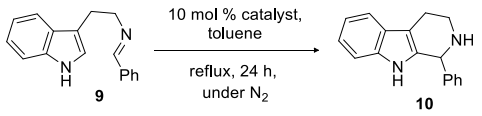
$CH_2P^tBu_2\}$]OTf (**1**), that enables hydrogen borrowing reactions with excellent functional group tolerance, including phenols and indoles.[16l,m] Herein we report the application of our strategy to the tandem alcohol amination/PSR.

The reaction between benzyl alcohol (**6**) and tryptamine (**7**) catalyzed by complex **1** can produce either *N*-benzyltryptamine (**8**) or *N*-benzylidenetryptamine (**9**).[16l] To realize the tandem sequence, imine **9** must be generated selectively as an intermediate, so we found that conducting the reaction in refluxing toluene gives a full conversion of **7** to **9** selectively (Table S1 and Figure S3). We next identified the conditions to cyclize **9** by screening Lewis acid catalysts (Table 1).[18] Metal

Table 1. Screening Lewis Acids for the Cyclization Step



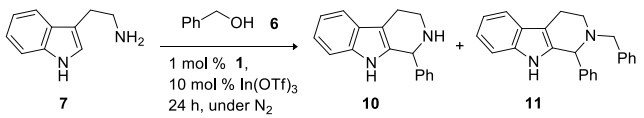
entry	catalyst	conversion (%)[a]
1	$CeCl_3$	22
2	$ScCl_3$	37
3	$FeCl_3$	41
4	$InCl_3$	52
5	$Y(OTf)_3$	88
6	$ZnBr_2$	92
7	$In(OTf)_3$	100

[a]Derived from ^{1}H NMR.

chlorides (entries 1–4) showed some activity, with imine hydrolysis as a competing reaction. $Y(OTf)_3$ and $ZnBr_2$ showed better activity (entries 5 and 6), and full conversion was achieved with $In(OTf)_3$ (entry 7).

After optimizing the two independent steps of our proposed synthetic sequence, we next turned to combining these steps in a tandem reaction (Table 2). Coupling **7** and **6** (1.5 equiv)

Table 2. Optimization of the Tandem Sequence



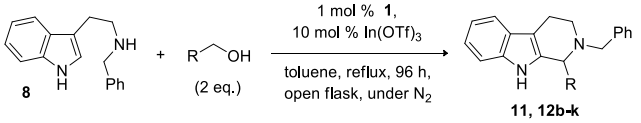
				yield (%)[a]	
entry	BnOH (equiv)	solvent	temp (°C)	**10**	**11**
1	1.5	toluene	120	43[b]	33[b]
2	2.5	toluene	120	39	36
3[c]	2.5	toluene	120	44	14
4	5	toluene	120		72
5	10	toluene	120		85
6	5	neat	110		81
7	10	neat	110		60

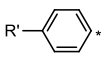
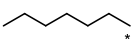
[a]NMR yield with mesitylene as the internal standard. [b]Yield is based on tryptamine. [c]**1**, **6**, and **7** were mixed and refluxed in toluene. After 24 h, 10% $In(OTf)_3$ was added and refluxed for another 24 h.

with 1% **1** and 10% $In(OTf)_3$ in toluene yields a mixture of the expected product **10** and its *N*-benzylated derivative **11** (entries 1–3). Surprisingly, the combined yield is reduced when we perform the reaction as a two-step synthesis in a single reactor (compare entries 2 and 3), although this afforded higher selectivity for **10**. Selectivity for **11** was optimized by increasing the concentration of benzyl alcohol (**6**): reactions with 5 or 10 equiv of **6** produced **11** exclusively (entries 4–7) with the added benefit of protecting the product amine.

With high-yielding conditions for the tandem process, we moved on to study its substrate scope. While reactions proceeding from the parent tryptamine afforded useful yields in many cases (Table S2), we found that side reactions of tryptamine frustrate material balance. Protecting tryptamine as its *N*-benzylamine (**8**) removes such side reactions and enables a broad substrate scope (Table 3). We found good functional

Table 3. Substrate Scope for the Tandem Sequence



entry	R[d]	product	yield (%)[a]
			
1	R' = H	**11**	73
2	R' = F	**12b**	70
3	R' = Br	**12c**	78
4	R' = *t*-Bu	**12d**	72
5	R' = SMe	**12e**	70
6	R' = CO_2Me	**12f**	51 (72)[b]
7	R' = OMe	**12g**	43
8		**12h**	56
9[c]		**12i**	47
10[c]		**12j**	70
11[c]		**12k**	55

[a]Isolated yield. [b]With CF_3COOH as the acid catalyst. [c]A mixture of *N*-benzyltryptamine (0.2 mmol), alcohol (1 mmol), styrene (1 mmol), **1** (1 mol %) and $In(OTf)_3$ (10 mol %) was stirred at 110 °C for 96 h in a closed reactor. [d]* shows the carbon in which CH_2OH is attached.

group tolerance among benzyl alcohols bearing fluoro, bromo, *tert*-butyl, and thioether groups at the para position, each affording the corresponding tetrahydro-β-carboline in a high yield (entries 2–5). Electron-withdrawing ester (entry 6) and thiophenyl groups (entries 8 and 11) are also well tolerated. Oddly, a reaction with methoxybenzyl alcohol was less successful (entry 7), even in cases where the respective coupling components were added slowly.

In addition to aryl and heteroaryl carbinols, various aliphatic alcohols participate in the tandem reaction under slightly modified conditions (Table 3, entries 9–11). This was unexpected, whereas we have recently reported that catalyst loadings well below 1 mol % are needed to enable alcohol amination with catalyst **1**.[16m] As the low boiling point of the

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aliphatic alcohols prevented us from running their reaction in an open reactor, we identified suitable closed reactor conditions incorporating styrene as a hydrogen acceptor.

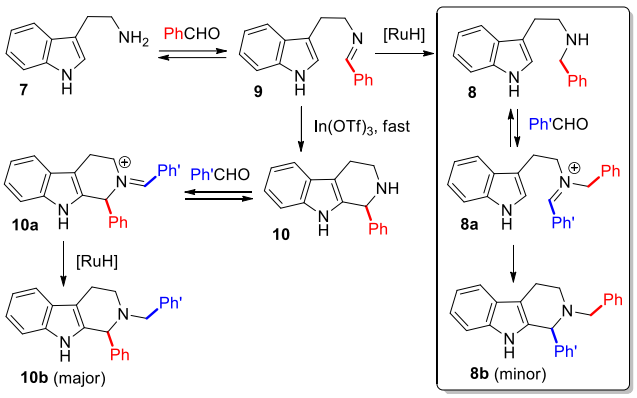
Introduction of the *N*-benzylamino group of **8** is not simply a strategy for improved yield: it is a versatile protecting group that enables differential substitution of this nitrogen through its convenient cleavage. While this deprotection has a potential complication of opening the newly formed piperidine ring, we find chemoselective cleavage of **11** with hydrogen and Pd/$BaSO_4$ to give **10** in 80% yield upon screening various heterogeneous hydrogenation catalysts (Table S6).

While our results demonstrate a unique combination of hydrogen borrowing amination conditions and the PSR, we thought it prudent to check whether the few other known hydrogen borrowing catalysts might also affect the tandem process. We screened iridium homologues of **1**, complexes **2** and **3** (Figure 1),[21] and base-free amination catalysts[17c,d] $[Cp^*IrCl_2]_2$ and $[Cp^*IrI_2]_2$. We found that each of these complexes returns starting materials, octanol and **8**, under the tandem conditions. Thus, ruthenium complex **1** is the only catalyst we find for the tandem sequence.

Since **8**, a secondary amine, is a convenient substrate for our reaction, the intermediate iminium ion resulting from its condensation with an aldehyde need not be further activated to enable cyclization. By contrast, imine of the parent tryptamine must be activated by a proton or Lewis acid. Oddly, reactions of **8** retain the need for the $In(OTf)_3$ cocatalyst, so we went about studying the mechanism[22] of our reaction to identify the role of the Lewis acid. We recently reported in detail the role of the metal catalyst in the amination,[16m] so we limit this discussion to the sequence of organic intermediates in the tandem process.

Pathways for the reactions starting from tryptamine (**7**) and *N*-benzyltryptamine (**8**) are shown in Scheme 1. In the first,

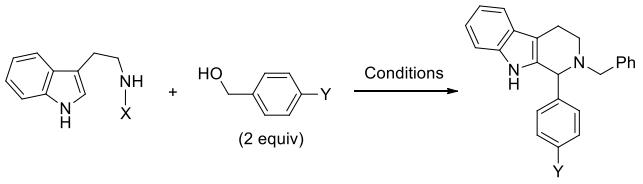
Scheme 1. Proposed Mechanisms for the Tandem Sequence



tryptamine undergoes condensation with benzaldehyde, generated in situ, to form **9**. It can either undergo ring closure in the presence of indium triflate to afford **10** or be reduced to **8**. We compared the relative rates of these potentially competing reactions by analyzing the product distribution in the reaction between **9** and 4-fluorobenzyl alcohol under the catalytic conditions (Scheme S1). We found that **9** converts to a mixture of 36% of **10** and 38% of **10b** and **8b** together, where Ph′ is a fluorophenyl group. This indicates that under the tandem conditions both **10b** and **8b** are formed and that the cyclization step (**9** to **10**) is faster than the imine reduction (**9** to **8**) and the second amination step (**10** to **10b**). This mechanism accounts for the crucial role of the Lewis acid and explains the distribution of products **10** and **11** observed in Table 2.

When the reaction proceeds from *N*-benzyltryptamine **8**, it can take only one pathway (highlighted on the right of Scheme 1). This sequence starts with the formation of iminium ion **8a**, followed by cyclization to give **8b**. This formal iminium ion is more electrophilic than the imine involved in the parent sequence. We perceive that this is one of the advantages of *N*-benzyltryptamine as a substrate for the tandem reaction. This sequence proceeds without an acid catalyst, albeit at lower yield (compare 32% to 73% (Table 4)), so indium is important

Table 4. Substituting $MgSO_4$ for $In(OTf)_3$ in the Tandem Sequence



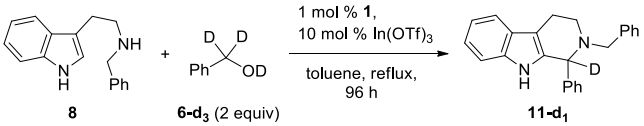
entry	X	Y	conditions	product and yield[a]
1	H	H	1 mol % **1**, 1 equiv of $MgSO_4$, neat, 110 °C, 24 h	**11** (20%)
2	H	H	1 mol % **1**, 10 mol % $In(OTf)_3$, neat, 110 °C, 24 h	**11** (79%)[b]
3	CH_2Ph	H	1 mol % **1**, no $In(OTf)_3$, neat, 110 °C, 24 h	**11** (32%)
4	CH_2Ph	H	1 mol % **1**, 10 mol % $In(OTf)_3$, toluene, reflux, 96 h	**11** (73%)[b]
5	CH_2Ph	Br	1 mol % **1**, 10 mol % $In(OTf)_3$, toluene, reflux, 96 h	**12c** (78%)[b]
6	CH_2Ph	Br	1 mol % **1**, 1 equiv of $MgSO_4$, toluene, reflux, 96 h	**12c** (74%)

[a]NMR yield with mesitylene as the internal standard. [b]Isolated yield.

but nonessential. When catalytic indium is replaced with 1 equiv of $MgSO_4$ in the reaction of **8** with 4-bromobenzyl alcohol, we see similar yields, 78% and 74%. In contrast, the parent tryptamine cyclization yielded product **11** in 20% yield with $MgSO_4$ compared to 79% with catalytic $In(OTf)_3$. We speculate that the role of indium or magnesium in reactions of **8** could be a dehydrating agent driving iminium formation, rather than Lewis acid promoting iminium activation.

Unlike the parent tryptamine reaction, two products are possible when *N*-benzyltryptamine reacts with an alcohol, because either the starting *N*-benzyl group or the added alcohol could potentially participate in the cyclization. We observe one product,[23] which has only the added alcohol participating in cyclization. Isotopic labeling supports this point (Scheme 2): reaction of **8** and benzyl alcohol-d_3, **6**-d_3, gives **11**-d_1 along with its ^1H isotopolog (ca. 25%), but no other labeled species. A ^2H NMR spectrum (Figure S15) of the isolated product shows a singlet at 4.67 ppm corresponding to the aliphatic CD position of **11**-d_1. No ^2H is observed at the

Scheme 2. Deuterium Labeling Experiment



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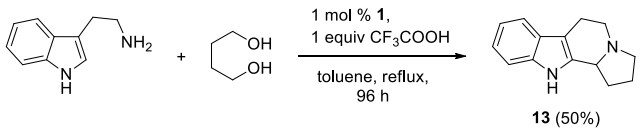
methylene positions of **11**-d_1 (3.89 and 3.37 ppm). The absence of $^1H/^2H$ scrambling combined with the reaction's selectivity for **8b** indicates that the hydride abstraction from **8** is prohibitively slow. This precludes our mechanism of all C−H oxidation pathways in which **8** is the hydride donor.

As a first step toward developing a biomimetic cascade sequence, we exhibit below a tandem reaction of tryptamine with 1,4-butanediol in the presence of 1 equiv of trifluoroacetic acid which yields the one-step total synthesis of harmicine (**13**), a natural product with antileishmanial[24] and antinociceptive[25] activity. The reaction connects three bonds and two rings in 50% yield overall (Scheme 3), with tryptamine's

Scheme 3. One-Step Synthesis of Harmicine



trifluoroacetamide (33%) as the sole side product (Table S5). Multistep synthesis of (*R*)-harmicine by enzyme catalysis has been reported.[26] Our method for the fused ring construction on the THBC core is an important platform for the alkaloid total synthesis in addition to being a remarkable example of two hydrogen-borrowing aminations in the presence of an acid.[27] Further studies aiming at more complex heterocycles in high yield are ongoing.

In conclusion, we report the catalytic, tandem synthesis of tetrahydro-β-carbolines from *N*-benzyltryptamine and alcohols. This method is applicable to benzylic alcohols, heterocycles, and aliphatic alcohols when styrene is used as a hydrogen acceptor. Our mechanistic studies suggest two separate pathways for reactions starting from tryptamine or *N*-benzyltryptamine. The latter case involves formation of a free iminium ion intermediate, so the role of the indium cocatalyst changes. H/D labeling shows that the secondary amine/imine equilibrium is prohibitively slow in our system. This governs the product selectivity for *N*-benzyltryptamine reactions. The tandem sequence enables the formation of the ABCD ring of indole alkaloids like harmicine in a single step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01485.

Experimental procedures, graphical and tabular characterization information (PDF)

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Notes

The authors declare no competing financial interest.

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