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Synthesis of tetrahydro- β -carbolines *via* isomerization of *N*-allyltryptamines: a metal-catalyzed variation on the Pictet–Spengler theme†

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An efficient and broadly applicable alternative to the classical Pictet–Spengler synthesis of tetrahydro- β -carbolines is presented. The method relies on metal-catalyzed isomerization of allylic amines to form reactive iminium intermediates which can be trapped by a tethered indole nucleophile.

The tricyclic 1,2,3,4-tetrahydro- β -carboline (THBC) ring system is a key structural element in a range of biologically and pharmacologically important alkaloids isolated from a variety of natural sources (Fig. 1).¹

THBCs are traditionally synthesized *via* the Pictet–Spengler reaction, where tryptamines are condensed with aldehydes under acidic reaction conditions.² We herein wish to report an alternative route to THBCs, which relies on metal-catalyzed isomerization of *N*-allyltryptamines (Fig. 2).

Metal-catalyzed double-bond isomerization of allylic amines to enamines has found widespread applications in organic synthesis.^{3–6}

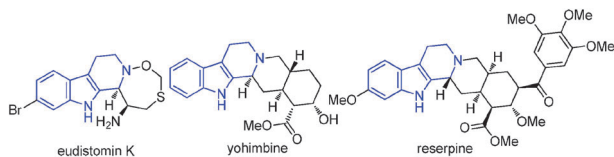


Fig. 1 THBC-containing natural products.

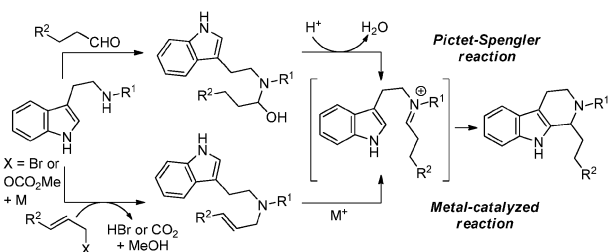


Fig. 2 Traditional Pictet–Spengler and new metal-catalyzed reactions in the synthesis of THBCs.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data for all substrates and products. See DOI: 10.1039/c2cc17704h

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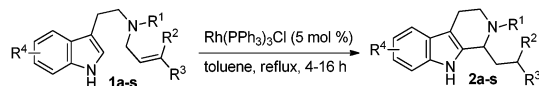
Surprisingly, the concurrent isomerization into synthetically useful iminium intermediates remains virtually unexplored. Along these lines, Sorimachi and Terada have reported a dual ruthenium hydride/Brønsted acid-catalyzed tandem process, where allylamines are isomerized to iminium intermediates that undergo Friedel–Crafts type reactions with electron-rich aromatics.^{7a} Similarly, we have recently demonstrated how cyclic allylic amines isomerize under the influence of Ru alkylidene catalysts to generate cyclic *N*-acyliminium intermediates useful for the synthesis of heterocyclic compounds.^{7b} These findings now lead us to propose allylic amines as convenient precursors for the metal-catalyzed formation of iminium ions which are commonly utilized intermediates in the synthesis of heterocyclic compounds, such as the present variation on the Pictet–Spengler theme.⁸

Initial investigations focused on the conversion of allylic amine **1a** to THBC **2a** (Table 1), where a range of Rh-, Pd-, and Ru-based catalysts was examined. Several catalysts in amounts of 1 mol% were shown to mediate a complete transformation within 23 h (Table 1, entries 1, 2, 8, and 9).

Table 1 Transition metal catalysts for the synthesis of THBC **2a** (selected results)^{a,b}

Entry	Catalyst	Conversion ^{c,d} (%)	
		6 h	23 h
1	Rh(PPh ₃) ₃ Cl	76	100 (33) ^e
2	RuHCl(CO)(PPh ₃) ₃	68	100 (14) ^e
3	Pd(PPh ₃) ₄	58	66
4	Pd(<i>i</i> -Bu) ₃	5	14
5	Grubbs II	95	95 (7) ^e
6	Hoveyda–Grubbs I	6	10
7	Hoveyda–Grubbs II	30	47
8	Ru(PCy ₃)(MPI)(PM)Cl ₂	95	100 (42) ^e
9	Ru(MPI)(<i>i</i> -PROPM)Cl ₂	100	100 (5) ^e

^a See the ESI for a full account on reaction optimization. ^b Abbreviations: MPI, 1,3-bis(2-methylphenyl)-2-imidazolidinylidene; PM, phenylmethylene; PRO, propoxy. ^c Determined by RP-HPLC (215 nm). ^d Product mixtures were generally very clean (>85% of **1a** and **2a** in the reaction mixture). ^e Reaction carried out with 0.1 mol% catalyst.

Table 2 Rh-catalyzed synthesis of THBCs

Entry	Substrate	R ¹	R ²	R ³	R ⁴	Product, yield ^a (%)
1	1a	Bn	H	H	H	2a , 90
2	1b	(4-NO ₂)C ₆ H ₄ CH ₂	H	H	H	2b , 86
3	1c	(3,4-(OMe) ₂)C ₆ H ₃ CH ₂	H	H	H	2c , 77
4	1d	CyCH ₂	H	H	H	2d , 86
5	1e	Heptyl	H	H	H	2e , 69
6	1f	Allyl	H	H	H	2f , 71
7	1g	Ph	H	H	H	2g , 49 ^b
8	1h	Me	H	H	H	2h , 75
9	1i	Bn	H	H	5-OMe	2i , 94
10	1j	Bn	H	H	6-OMe	2j , 76
11	1k	Bn	H	H	7-Me	2k , 80
12	1l	Bn	H	H	5-Me	2l , 81
13	1m	Bn	H	H	5-F	2m , 42
14	1n	Bn	H	H	5-Br	2n , 68
15	1o	Bn	Me	Me	H	2o , 26 ^{b,c}
16	1p	Bn	H	Me	H	2p , 71 ^b
17	1q	Bn	H	Ph	H	2q , 65
18	1r	Bn	H	(4-NO ₂)C ₆ H ₄	H	2r , 43 ^b
19	1s	Bn	H	(4-OMe)C ₆ H ₄	H	2s , 59 ^b

^a Isolated yield after flash column chromatography. ^b Reaction carried out with 15 mol% catalyst. ^c 51% yield, when using 30 mol% catalyst and 60 mol% *n*-BuLi.⁹

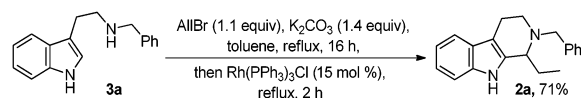
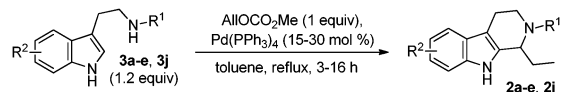
A reduction of the loading to 0.1 mol% clearly identified Wilkinson's catalyst (Table 1, entry 1) and Ru alkylidene catalyst Ru(PCy₃)(MPI)(PM)Cl₂ (Table 1, entry 8) as most efficient. In control experiments with catalytic amounts of acid, such as TFA, and absence of catalyst, no conversion of starting material could be detected, which points to a unique role of the metal catalyst. When applied to a range of readily available *N*-alkyl-*N*-allyltryptamines, Wilkinson's catalyst proved to be highly efficient (Table 2). THBCs **2a–s** were obtained in 26–94% yield. Variation of R¹ and the indole substitution pattern did not significantly affect the reaction (Table 2, entries 1–14). On the other hand, the *N*-allylic substituent pattern greatly influenced reactivity (Table 2, entries 15–19), and some substrates (**1g**, **1o–p** and **1r–s**) needed up to 15 mol% of catalyst to achieve high substrate conversion and isolated product yields.

The successful metal-catalyzed double bond isomerization reactions may stimulate the development of asymmetric variants. Much recent work has indeed been dedicated to asymmetric Pictet–Spengler-type reactions.^{2a} To this end, we briefly investigated Ru-catalysis with chiral ligands, and cooperative catalysis of metals and chiral Brønsted acid for the reaction (see ESI†). Unfortunately, these preliminary experiments did not reveal any signs of asymmetric induction. The classical Pictet–Spengler reaction of tryptophan esters with aldehydes typically proceeds with limited diastereocontrol in the synthesis of 1,3-disubstituted tetrahydro-β-carbolines. The stereochemical outcome is highly dependent on both reaction conditions and the stereoelectronic nature of the reactive amine and aldehyde components.¹⁰ It was therefore interesting to examine if the action of Wilkinson's catalyst in the event of iminium ion formation could influence the diastereoselectivity of the cyclization step. Unfortunately, the methyl ester of *N*-benzyl-*N*-allyltryptophan did not undergo any significant conversion under the reaction conditions shown in Table 2, and only traces of the THBC product were detected

by LC/MS analysis. Evidently, the action of this catalyst may be sensitive to the steric congestion posed by the ester moiety, and/or the reduced nucleophilicity of the intermediate iminium nitrogen atom.

The methodology was also extended to a sequential reaction process (Scheme 1), where secondary tryptamine **3a** was allylated before adding Wilkinson's catalyst, ultimately providing THBC **2a** in good yield.

Finally, to provide a one-pot sequence analogous to the Pictet–Spengler reaction, a tandem Tsuji–Trost/isomerization/iminium cyclization approach was demonstrated (Table 3).^{11,12} A range of readily available secondary tryptamines (**3a–e** and **3j**)

**Scheme 1** Synthesis of THBC **2a** via a one-pot allylation/isomerization/cyclization sequence.**Table 3** Synthesis of THBCs via a Pd-catalyzed Tsuji–Trost/isomerization/iminium cyclization sequence

Entry	Substrate	R ¹	R ²	Product, yield ^a (%)
1	3a	Bn	H	2a , 85
2	3b	(4-NO ₂)C ₆ H ₄ CH ₂	H	2b , 86
3	3c	(3,4-(OMe) ₂)C ₆ H ₃ CH ₂	H	2c , 81
4	3d	CyCH ₂	H	2d , 67
5	3e	Heptyl	H	2e , 48
6	3j	Bn	6-OMe	2j , 67

^a Isolated yield after flash column chromatography.

could be efficiently converted to THBCs (48–86%) when reacted with allylmethylcarbonate and Pd(PPh₃)₄ in refluxing toluene.

In summary, we have shown that metal-catalyzed tandem isomerization/cyclization of *N*-allyltryptamines constitutes an efficient alternative to the Pictet–Spengler reaction for the synthesis of THBCs. Several metal catalysts were shown to mediate the transformation, and the strategy thus points to an underexplored role of metal catalysts in iminium chemistry. At this stage, it must be emphasized that the proposed mechanism (Fig. 2) for the reaction process is merely tentative and will be subject of future research. Notably, when using a Pd catalyst, THBCs can be synthesized *via* a novel one-pot tandem process that involves Pd-catalyzed Tsuji–Trost reaction, isomerization, and *N*-alkyliminium cyclization, thus providing a metal-catalyzed variant of the Pictet–Spengler reaction.

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