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Highly Enantioselective Synthesis of Tetrahydro- $\beta$ -Carbolines and Tetrahydro- $\gamma$ -Carbolines Via Pd-Catalyzed Intramolecular Allylic AlkylationMarco Bandini,\* Alfonso Melloni,<sup>†</sup> Fabio Piccinelli, Riccardo Sinisi, Simona Tommasi, and Achille Umani-Ronchi\*Dipartimento di Chimica "G. Ciamician", Alma Mater Studiorum,  
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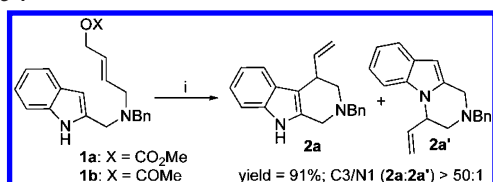
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The astonishing growth of worldwide sales of stereochemically defined pharmacological compounds calls for continuous research addressed toward the development of novel and always more effective asymmetric synthetic strategies.<sup>1,2</sup>

1,2,3,4-Tetrahydro- $\beta$ -carbolines (THBCs) represent a deeply investigated family of indole-containing alkaloids that possess a wide diversity of important medicinal activities.<sup>3</sup> The condensation of tryptophan or tryptamine derivatives with carbonyls, under acidic conditions (Pictet–Spengler, PS reaction),<sup>4</sup> still represents the primary route to the preparation of this prominent class of biologically active compounds. Herein, after the pioneering paper published almost one century ago, several milder diastereoselective versions have been reported;<sup>5a,b</sup> however, only one example of catalytic enantioselective PS condensation has been described to date.<sup>6</sup>

Despite the wide scope of the PS condensation, it turns out to be less straightforward when 4-substituted THBC systems are targeted.<sup>7</sup> In these cases, in fact, time-demanding procedures for the synthesis of appropriate  $\beta$ -substituted tryptamine precursors are needed, and even more challenging synthetic approaches must be contemplated to achieve enantiomerically pure molecules.

As a part of our research interest addressed toward the investigation of new catalytic chemo-, regio-, and stereocontrolled Friedel–Crafts-type (FC) alkylation of indoles,<sup>8</sup> we recently reported on the use of Pd-catalyzed intramolecular allylic alkylation as an alternative procedure to the conventional FC strategies.<sup>9</sup> The optimized catalytic conditions allowed inter- as well as intramolecular allylic alkylation of variously functionalized indoles to be performed with high yield and in highly regioselective manner, simply by properly choosing reaction media and base additive. Notably, the intramolecular variant (C3-alkylation), starting from the readily synthesizable indolyl carbonate **1a**, furnished regioselectively polycyclic fused indoles, such as 4-vinyl-THBC, **2a**, in high yield (Scheme 1).

Scheme 1<sup>a</sup>

<sup>a</sup> Reagents and conditions: (i) [PdCl( $\pi$ -allyl)]<sub>2</sub> (5 mol %), PPh<sub>3</sub> (22 mol %), BSA (2 equiv), Li<sub>2</sub>CO<sub>3</sub> (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt.

The present paper will detail a practical and flexible alternative to the PS methodology, based on the use of intramolecular Pd-catalyzed asymmetric allylic alkylation (AAA, Trost reaction)<sup>10</sup> for the synthesis of 4-vinyl-THBCs in high optical purity. Moreover,

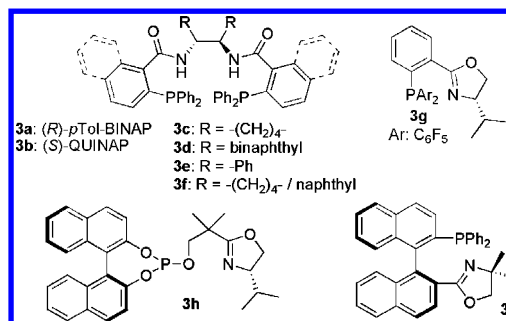


Figure 1.

Table 1. Optimization of the Reaction Conditions for the Intramolecular AAA of **1a**<sup>a</sup>

entry	L*	1	2a yield (%) <sup>b</sup>	2a ee (%) <sup>c</sup>	2a/2a' <sup>d</sup>
1	(R)- <b>3a</b>	<b>1a</b>	43	46 (S) <sup>e</sup>	> 50:1
2	(S)- <b>3b</b>	<b>1a</b>	73 <sup>f</sup>	21 (R)	> 50:1
3	(R,R)- <b>3c</b>	<b>1a</b>	90	82 (R) <sup>g</sup>	19:1
4	(S)- <b>3d</b>	<b>1a</b>	88	74 (S)	> 50:1
5	(S,S)- <b>3e</b>	<b>1a</b>	88	92 (R)	> 50:1
6	(S,S)- <b>3e</b>	<b>1b</b>	90	90 (R)	> 50:1
7	(R,R)- <b>3f</b>	<b>1a</b>	88	72 (R)	> 50:1
8	(S)- <b>3g</b>	<b>1a</b>	> 95	30 (S) <sup>e</sup>	> 50:1
9	(R,S)- <b>3h</b>	<b>1a</b>	> 98	20 (S) <sup>e</sup>	> 50:1
10	(R)- <b>3i</b>	<b>1a</b>	95	66 (R) <sup>h</sup>	12:1

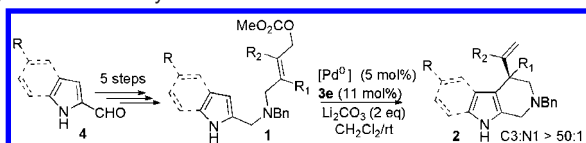
<sup>a</sup> All the reactions were carried out in anhydrous CH<sub>2</sub>Cl<sub>2</sub> at room temperature, by using 5 mol % of [Pd<sub>2</sub>(dba)<sub>3</sub>]·CHCl<sub>3</sub>, 11 mol % of L\*, and 2 equiv of Li<sub>2</sub>CO<sub>3</sub>. Reaction time was 16 h. <sup>b</sup> Isolated yields after flash chromatography. <sup>c</sup> Determined by chiral HPLC analysis. The absolute configuration was determined by X-ray analysis (see Supporting Information). <sup>d</sup> Determined by HPLC. <sup>e</sup> Under reflux, 16 h. <sup>f</sup> Reaction time 7 days. <sup>g</sup> Enantiomeric excess of **2a'** = 60%. <sup>h</sup> Enantiomeric excess of **2a'** = 61%.

the present catalytic system is described to be effective also in promoting the synthesis of tetrahydro- $\gamma$ -carbolines (THGCs, **7**)<sup>11</sup> with high stereoselectivity.

By virtue of the readily synthetic availability, **1a** was chosen as the model substrate, and a brief survey of intramolecular AAA conditions, by using both C1- and C2-symmetrical P/P and P/N “privileged ligands” (**3a**–**i**), was performed (Figure 1).<sup>12</sup>

A representative collection of results is summarized in Table 1. First, among all the chiral promoters employed, the DPPBA-based ligands (**3c**–**f**), commonly known as Trost’s ligands, furnished the highest level of regio- and stereoselectivity (entries 3–7, Table 1).<sup>13</sup> In this context, we were particularly delighted to discover that diphenyl derivative (S,S)-**3e** furnished the desired (R)-4-vinyl-THBC **2a** in 88% isolated yield and 92% ee. Moreover, the stereochemical reaction outcome was not affected by the nature of the leaving group. As a matter of fact, when 2-indolyl allyl acetate **1b** was employed, **2a** was isolated in comparable yield (90%) and enan-

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**Table 2.** Proving the Generality of the Intramolecular AAA for the Synthesis of 4-Vinyl-THBCs

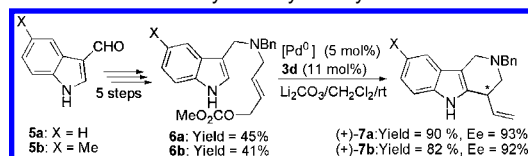
entry	4	R/R <sub>1</sub> /R <sub>2</sub>	1 yield (%) <sup>a</sup>	2 yield (%) <sup>b</sup>	2 ee (%) <sup>c</sup>
1	<b>4a</b>	H/H/H	<b>1a</b> (33)	<b>2a</b> (88)	92 ( <i>R</i> )
2	<b>4b</b>	OMe/H/H	<b>1c</b> (37)	<b>2c</b> (95)	90 ( <i>R</i> )
3	<b>4b</b>	OMe/H/H	<b>1c</b> (37)	<b>2c</b> (60) <sup>d</sup>	94 ( <i>R</i> )
4	<b>4d</b>	Cl/H/H	<b>1d</b> (52)	<b>2d</b> (80)	82 ( <i>R</i> )
5	<b>4e</b>	Me/H/H	<b>1e</b> (41)	<b>2e</b> (98)	97 ( <i>R</i> )
6	<b>4f</b>	pyrrole/H/H	<b>1f</b> (28)	<b>2f</b> (85)	95 (—)
7	<b>4a</b>	H/Me/H	<b>1g</b> (19)	<b>2g</b> (45) <sup>e</sup>	90 (—)
8	<b>4a</b>	H/H/Me	<b>1h</b> (25)	<b>2h</b> (49) <sup>f</sup>	94 (—)

<sup>a</sup> Overall yield of five steps. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by chiral HPLC analysis. Absolute configuration assigned by analogy. <sup>d</sup> Reaction temperature was 0 °C. <sup>e</sup> Reaction carried out under reflux. <sup>f</sup> **3c** was used as ligand.

tiomeric excess (90%, entry 6). Finally, the absolute configuration of C4 in **2a** was unambiguously determined to be *R* by X-ray analysis (see the Supporting Information).

Having identified a useful set of reaction conditions, we carried out a study of substrate scope by performing the enantioselective cycloalkylation of a series of (*E*)-5-substituted indolyl carbonates (**1c–h**) that were obtained from the corresponding aldehydes **4b–e**.

Remarkable tolerance toward steric and electronic demands of substituents in the indole carbonate precursors was shown (Table 2). In particular, the presence of electron-donating groups (**1c**, **1e**) delivered (*R*)-4-vinyl-THBCs<sup>14</sup> in good yields and high enantiomeric excesses ranging from 90 to 97%. The scope of the process was further extended to the synthesis of pyrrolyl-based polycyclic systems, obtaining the **2f** in 85% yield and 95% ee (entry 6). Interestingly, quaternary stereocenters were also accessible through this new approach (90% ee, entry 7), and excellent stereoinduction was also obtained in the cyclization of substituted **1h** leading to **2h** in 94% ee (entry 8). Next, sequential intramolecular catalytic AAA was also effectively applied to indolyl carbonates **6a,b**, readily prepared by analogous multistep sequence, starting from commercially available 3-indole carbaldehydes **5**. Notably, also in these cases, the combined use of [Pd<sub>2</sub>dba<sub>3</sub>] $\cdot$ CHCl<sub>3</sub> and **3e** in anhydrous CH<sub>2</sub>Cl<sub>2</sub> provided the corresponding 1-vinyl-THGCs **7** in good yield, high regiochemistry (C3/N1 > 50:1), and excellent enantiomeric excess (92–93%, Scheme 2). To our knowledge, this methodology represents the first enantioselective metallo-catalyzed synthesis of functionalized tetrahydro- $\beta$ -carboline and tetrahydro- $\gamma$ -carboline. Interestingly, olefin geometry of the substrate **6** was found to strongly influence the stereochemistry of the reaction course. In fact, when (*Z*)-**6a** was reacted in the presence of (*S,S*)-**3e**, **7a** of opposite configuration was obtained (yield = 65%), but with modest enantiomeric excess (5%). This evidence could be rationalized by considering the *syn-anti* isomerization of the  $\pi$ -allylpalladium

**Scheme 2.** Highly Enantioselective Synthesis of 1-Vinyl-THGCs via Intramolecular Pd-Catalyzed Allylic Alkylation of Indoles

intermediate derived by (*Z*)-**6a**, slightly faster than the corresponding epimerization event.<sup>15</sup>

In summary, we present a new versatile and practical Pd-catalyzed reaction for the synthesis of 4-vinyl-THBCs and 1-vinyl-THGCs, via regioselective intramolecular AAA. The excellent levels in terms of yield and enantiomeric excess recorded suggest this strategy as a valuable candidate for the preparation of several classes of stereochemically defined polycyclic aromatic compounds.

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**Supporting Information Available:** Experimental procedures, spectral data for all the new compounds. CIF file of the crystal data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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