



## [(S)-BINAP]PdBr<sub>2</sub>-catalyzed direct synthesis of 2,3-disubstituted indoles via a tandem reaction between arylamines and α-diketones

A. Cabrera\*, P. Sharma, M. Ayala, L. Rubio-Perez, Manuel Amézquita-Valencia

Instituto de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Circuito Exterior, Coyoacán 04510, México D.F., Mexico

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### ABSTRACT

A direct PdBr<sub>2</sub>(BINAP)-complex catalyzed method has been developed to produce 2,3-disubstituted indoles by the reaction of arylamines with α-diketones under reductive (H<sub>2</sub>) conditions. The synthetic methodology involves a tandem reaction of three steps and all the organic intermediates were isolated and characterized, the reduction products in this sequence are chiral and present interesting enantiomeric excess. This report constitutes a new and different route to synthesize indoles and a plausible mechanism is also suggested.

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### Introduction

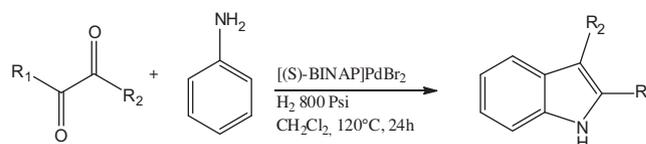
Substituted indoles are common and important heterocyclic compounds found in nature,<sup>1</sup> the indole moiety is present in a range of pharmaceutical agents and materials. Substituted indoles participate in different biological functions including as building blocks for proteins. Among the several types of substituted indoles, C(2)–C(3) substituted indoles are of special interest because these compounds are important promising therapeutic agents<sup>2</sup> and display antiestrogen antagonist, antiinflammatory, and cytotoxic properties. Various synthetic methods are reported in the literature for substituted indoles,<sup>3–5</sup> in the past years palladium-catalyzed syntheses of substituted indoles using C–C and C–X bond forming routes are reported.<sup>5b</sup> Annulation of 2-iodo-anilines and disubstituted alkynes a pioneering work of Larock,<sup>6</sup> cyclization of β-(2-iodophenyl) unsaturated ketones or esters a report by Sakamoto,<sup>7</sup> Heck cyclization of bromoenaminones reported by Chen et al.,<sup>8</sup> the intramolecular Heck cyclization of aryl iodides reported by Tietze<sup>9</sup> are some of the reports that can be cited in this context. Recently heteroannulation of 2-haloaniline and phenyl acetylene to produce 2-substituted indole derivatives reported by Oskooie et al.,<sup>2</sup> and a recent communication of Cacchi et al. on palladium-catalyzed synthesis of 2,3-disubstituted indoles from arenediazonium tetrafluoroborates and 2-alkynyltrifluoro acetanilides<sup>10</sup> are some other reports that also mention the palladium-catalyzed syntheses of these heterocycles. Although a number of routes for indole synthesis

have been reported, the development of new methods for the synthesis of indoles remains an active area of research, here we report for the first time a new tandem catalytic way to synthesize indoles.

### Results and discussion

In continuation to our research on the synthesis of chiral aromatic amines by direct asymmetric reductive amination of carbonyl compounds,<sup>11</sup> using air stable preformed chiral palladium–phosphine complexes, a new direct method has been found for the synthesis of 2,3-disubstituted indoles by the heteroannulation of α-diketones and aromatic amines, via a homogeneous C–H activation of aromatic amines, in the presence of hydrogen pressure (Scheme 1). The C–H activation is one of the most interesting research fields in palladium-catalyzed annulation.<sup>12,13</sup>

A very good yield of indole derivatives was obtained when symmetric substrates were used, but when non-symmetric α-diketones were used (Table 1, entries 2 and 3), only one of the two possible products is obtained and the more substituted C-2 product is



**Scheme 1.** Formation of 2,3-disubstituted indoles via reductive amination of α-diketones with aniline.

\* Corresponding author.

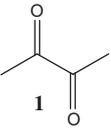
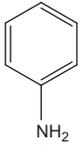
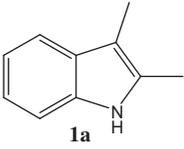
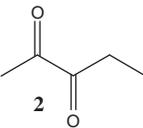
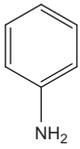
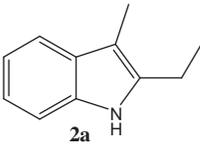
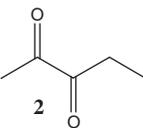
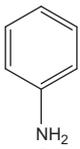
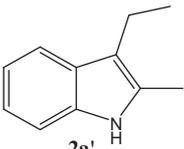
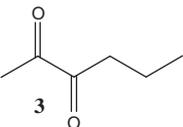
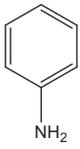
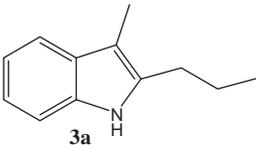
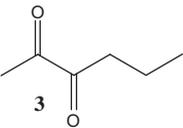
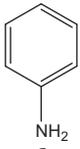
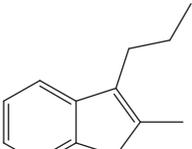
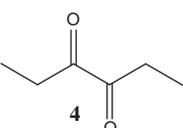
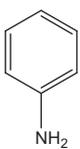
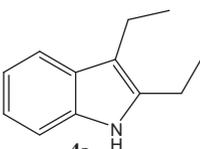
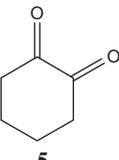
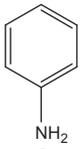
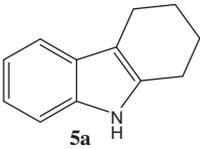
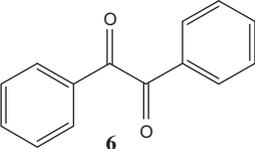
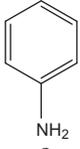
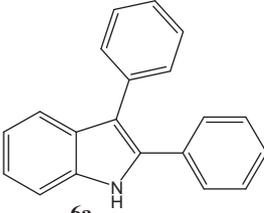
E-mail address: [arcaor1@servidor.unam.mx](mailto:arcaor1@servidor.unam.mx) (A. Cabrera).

preferred. This preference suggests that the final annulation step is highly sterically dependent and in consequence, the cyclization proceeds via the nucleophilic addition to less sterically hindered carbonyl group.

When *p*-anisidine was reacted with a symmetric  $\alpha$ -diketone viz. benzil (PhCOCOPh) an expected indole (Table 1, entry 7) was obtained along with imine (**12a**). But in this reaction no reduction

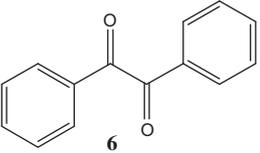
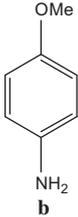
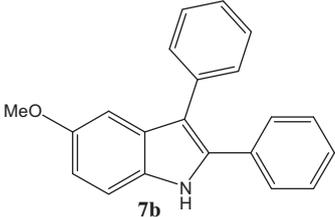
product of imine was observed, probably because the involvement of non-bonding electrons on *p*-methoxy group, gives an electron-delocalization extended until the second phenyl group. This will affect the C=N bond which becomes more conjugated, consequently a retardatory effect on hydrogenation rate of this imine must be observed. Compound (**12a**) was formed as an intermediate in the reaction and was isolated and characterized (Fig. 1).

**Table 1**  
Synthesis of 2,3-disubstituted indole from  $\alpha$ -diketones and aromatic amines

Entry <sup>a</sup>	$\alpha$ -Diketone	Amine	Product	Yield <sup>b</sup> (%)
1 <sup>c</sup>				100
2 <sup>c</sup>				98
2 <sup>c</sup>				Traces
3 <sup>c</sup>				95
3 <sup>c</sup>				Traces
4 <sup>d</sup>				100
5 <sup>c</sup>				100
6 <sup>d</sup>				99

(continued on next page)

Table 1 (continued)

Entry <sup>a</sup>	$\alpha$ -Diketone	Amine	Product	Yield <sup>b</sup> (%)
7 <sup>d</sup>				40

<sup>a</sup> Reaction conditions:  $\alpha$ -diketone (1 mmol), amine (1 mmol), H<sub>2</sub> (800 psi), [(S)-BINAP]PdBr<sub>2</sub> (0.025 mmol), temp 120 °C, CH<sub>2</sub>Cl<sub>2</sub> (10 mL).

<sup>b</sup> Determined by GC–MS analysis.

<sup>c</sup> 24 h.

<sup>d</sup> 48 h.

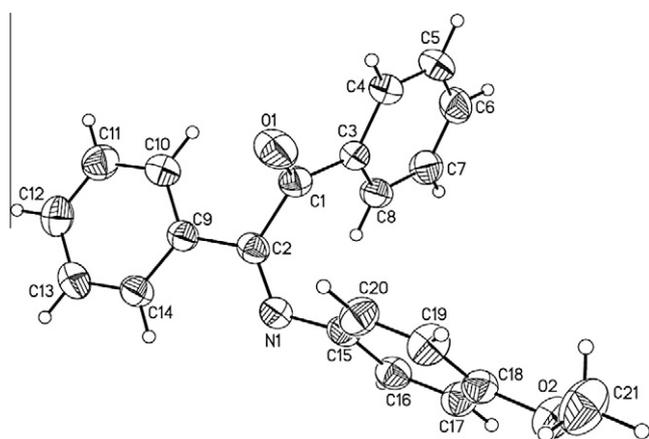


Figure 1. Thermal ellipsoid plot of imine **12a** (40% probability).<sup>14</sup>

When the reaction time was lowered from 48 to 24 h for substrate **6** (entry 11, Table 2) a chiral amine intermediate **11a** was isolated and characterized. This procedure was extended to other substrates, and an interesting chiral induction in these reaction products was observed (Table 2), this suggests the additional possibility to synthesize chiral indolines via an additional hydrogenation step,<sup>15</sup> with this catalytic system.

Based on these results, we report a novel direct synthesis of 2,3-disubstituted indoles which involves three steps viz. mono amination of  $\alpha$ -diketone giving an imine intermediate followed by a catalytic reduction giving chiral amine and final annulation–dehydration reaction to obtain the indole. It is shown schematically in Scheme 2.

One proposed pathway to account for these palladium-catalyzed reaction is offered in Scheme 3, although details await further investigations. Reductive amination of  $\alpha$ -diketone gives aminoketone **I** in equilibria with its tautomeric form **II** which is activated by the metallic species forming a palladacyclic complex as suggested in Pd-catalyzed cyclization of oxime acetates<sup>13</sup> followed of reductive elimination to give the indole derivative.

Table 2  
Formation of  $\alpha$ -amino ketones intermediates in the synthesis of 2,3-disubstituted indoles

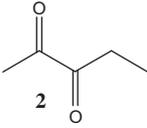
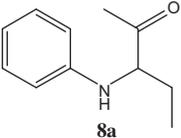
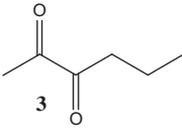
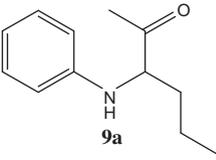
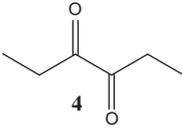
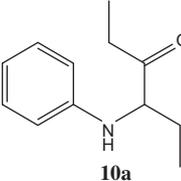
Entry <sup>a</sup>	$\alpha$ -Diketone	Amine	Intermediate	Time (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
8				12	70	73
9		<b>a</b>		12	73	96
10		<b>a</b>		12	90	1

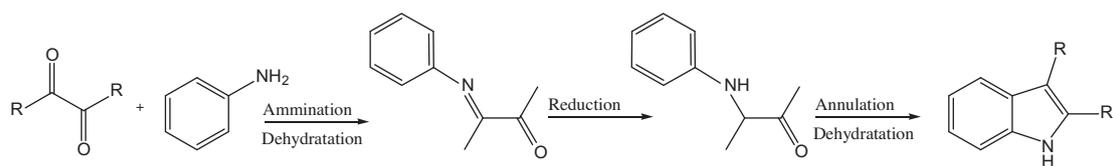
Table 2 (continued)

Entry <sup>a</sup>	$\alpha$ -Diketone	Amine	Intermediate	Time (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
11		<b>a</b>		24	79	82

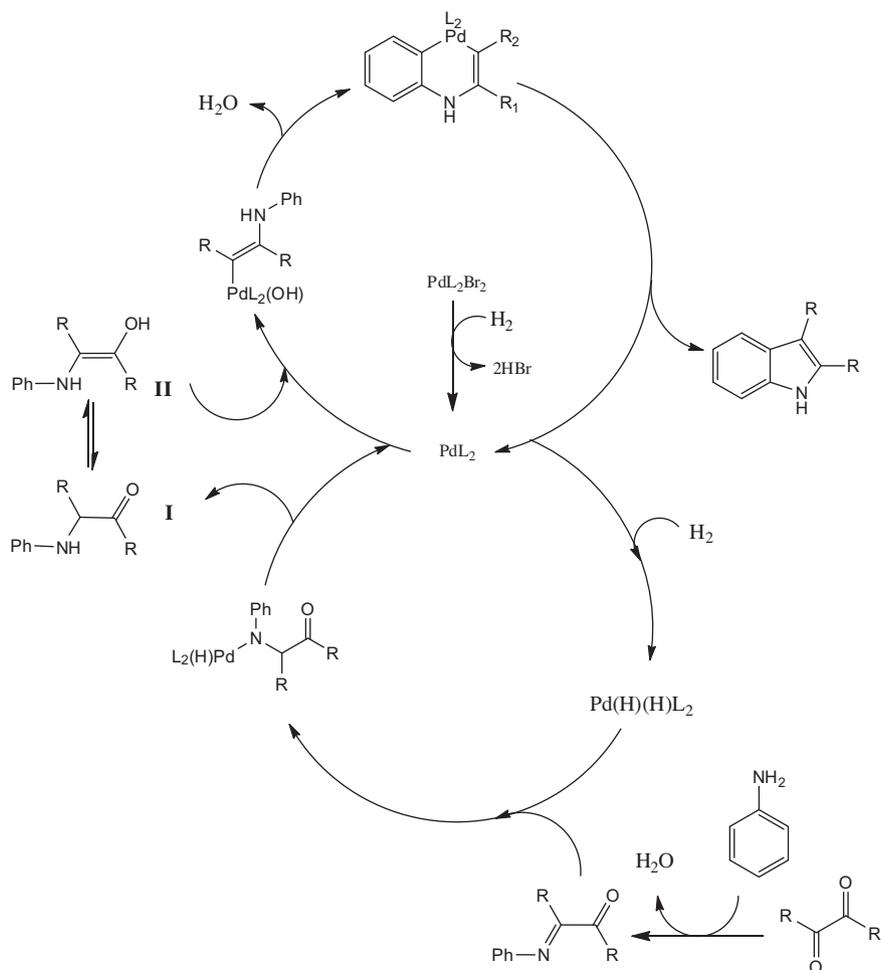
<sup>a</sup> Reaction condition:  $\alpha$ -diketone (1 mmol), amine (1 mmol), H<sub>2</sub> (800 psi), [(S)-BINAP]PdBr<sub>2</sub> (0.025 mmol), temp 120 °C, CH<sub>2</sub>Cl<sub>2</sub> (10 mL).

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by HPLC analysis with Daicel chiralcel OD-H column.



**Scheme 2.** Direct three step formation of 2,3-disubstituted indole via reductive amination annulation process.



**Scheme 3.** Suggested pathway for indole synthesis.

## Conclusion

A palladium-catalyzed alternative procedure to obtain 2,3-disubstituted indoles from  $\alpha$ -diketones, in very good yields is reported. Further studies on the effect of substituent groups on the nucleophilic amines and the confirmation of the mechanism proposed for this process are in progress.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2011.10.025](https://doi.org/10.1016/j.tetlet.2011.10.025).

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