Synthesis of Indoles by Palladium-Catalyzed Reductive Cyclization of β-Nitrostyrenes with Carbon Monoxide as the Reductant.

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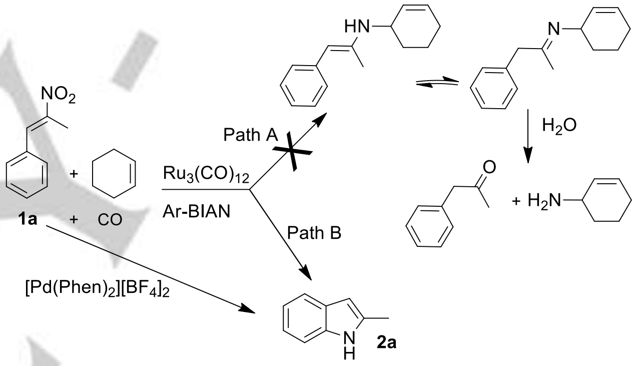
Abstract: An efficient catalytic cyclization of β-nitrostyrenes to indoles has been developed. The reaction was applied to the synthesis of 3-arylindoles and 2-alkylindoles. Since in the latter case the starting β-nitrostyrene can be easily obtained by a Henry reaction, the present method allows to obtain indoles in a two-step sequence starting from cheap reactants.

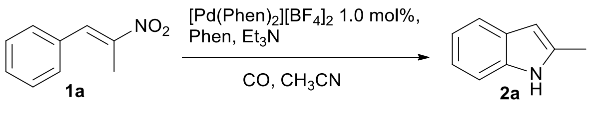
The indole skeleton is central to many biologically active pharmaceutical drugs and natural alkaloids [1] and its synthesis continues to attract the attention of many researchers.[2] Many syntheses of indoles are catalyzed by transition metals, but in most cases they require substrates bearing two suitable functional groups *ortho* to each other and the preparation of these starting materials often requires several synthetic steps. An example relevant for this work is the reductive cyclization of *o*-nitrostyrenes to indoles catalyzed by Pd/phosphine/$SnCl_2$,[3] Pd/phosphine[4] and Pd/phenanthroline[5] systems. Several years ago, we were investigating the possibility of using β-nitrostyrenes as aminating agents for olefins, employing a protocol previously devised for nitroarenes,[6] based on the use of a ruthenium/bis(aryl)acenaphthenequinonediimine (Ar-BIAN) catalyst. The aim was to obtain a vinylic amine that, after tautomerization, may be easily hydrolyzed, resulting in an overall introduction of an -NH_2 group in the allylic position (Scheme 1, Path A). Despite some efforts, we never observed the formation of the allylic amine. A mixture of products was obtained, among which 2-methylindole was always present (Scheme 1, Path B).

The deoxygenative cyclization reaction of β-nitrostyrenes to indoles has been reported in the literature to occur with $P(OEt)_3$ as the reducing agent only when the *alpha* position of the styrene bears a substituent, most commonly a second aryl group.[7] The reaction is only of little interest due to the need for a very large excess of trialkylphosphite and the consequent difficulty in its elimination from the product. No method has been reported in the literature for the efficient deoxygenative cyclization of **1a** or related β-nitrostyrenes lacking additional substituents in the *alpha* position.[8] The possibility of conducting the reaction under catalytic conditions intrigued us since the use of β-nitrostyrenes as substrates in indole synthesis is very interesting. In fact, in most cases, they can be easily prepared from an aldehyde and a nitroalkane by the Henry reaction, overcoming the problems associated to complex preparation of the substrates.



Scheme 1. Palladium and ruthenium catalyzed cyclization of β-methyl-β-nitrostyrene.

The indole yield was low using the catalytic system based on ruthenium, but better results were obtained employing $[Pd(Phen)_2][BF_4]_2$ in the presence of excess 1,10-phenanthroline (Phen). This system was previously reported to give very good results in other carbonylation reactions, such as the reductive carbonylation of nitroarenes[9] and several types of inter- and intra-molecular reductive cyclization reactions of nitroarenes.[5b, 10]



Scheme 2. Palladium catalyzed reductive cyclization of **1a** by CO.

Encouraged by these preliminary results, we optimized the reaction conditions employing the commercially available *trans*-β-methyl-β-nitrostyrene (**1a**) as a model substrate (Scheme 2, Table S1). The main results of the optimization study are the following:

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1) After an initial screening of solvents (*i.e.* DMF, THF, toluene), CH_3CN was identified as the best solvent.

2) The reaction does not need any co-catalyst to proceed but the addition of an organic base led to an enhancement in the system activity and indole selectivity. 1,4-Diazabicyclo[2.2.2]octane and triethylamine were tested and the latter gave higher selectivities. The concentration of the base was preliminarily optimized and best results were obtained at $[Et_3N] = 0.17$ M.

3) The selectivity in indole is almost independent from the CO pressure between 20 and 40 bar; however the reaction is strongly inhibited over 40 bar while the indole selectivity decreases at pressures lower than 20 bar.

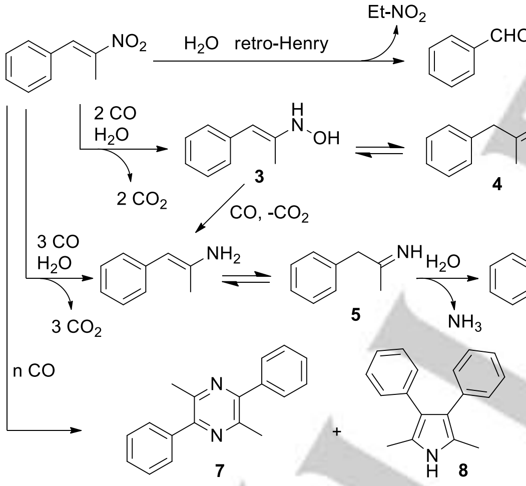
4) The selectivity is almost constant in the range 150 – 170 °C but decreases at lower temperatures.

5) Complete conversion was reached after 2.5 hours after which only decomposition of the product occurs.

6) The amount of phenanthroline was also optimized and best results were obtained with [Phen] = 0.012 M.[11]

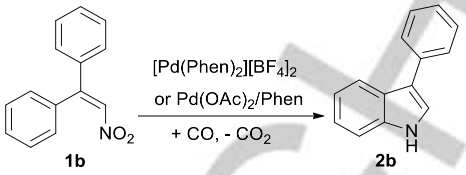
Using the optimized conditions, we were able to completely convert **1a** into **2a** with an 88% selectivity (measured by gas-chromatography Table S1, entry 5) and to isolate the product[12] with just a 2% loss with respect to the GC yield.

We have previously mentioned that the cyclization of **1a** to **2a** using $P(OEt)_3$ as the reductant is not known. To test if indole can be obtained by this methodology to some extent, we heated **1a** at 150 °C in neat $P(OEt)_3$. A mixture of products was obtained, among which the indole was not present (GC analysis, detection limit <1%).



Scheme 3. Side-products formation pathways for substrate **1a**

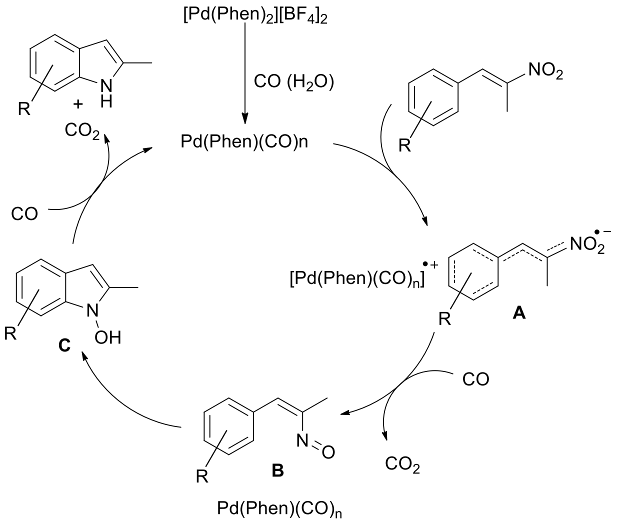
During the optimization study, we were able to identify by GC-MS some of the side products of the reaction. Under the optimized condition, their amount is very low and it was not possible to quantify them. The likely pathways of formation of these side products are reported in Scheme 3. Compounds **7** and **8** may derive from the dimerization of a radical anionic intermediate;[13] the dimer is then further reduced by carbon monoxide. The formation of **8** was previously reported to occur when β-nitrostyrenes are reduced with aqueous $TiCl_3$.[13] Even if the formation of the above mentioned side products can be almost suppressed under the optimized conditions, some unidentified high-boiling side-products still form to some extent.



Scheme 4. Palladium catalyzed reductive cyclization of **1b**.

A few years ago, Hsieh and Dong reported a study on the palladium-catalyzed reductive cyclization of α-aryl-β-nitrostyrenes.[14] $Pd(OAc)_2$ was used as the catalyst, the molar ratio of cat/Phen/substrate was 1:2:50 and the reaction was carried out in DMF, at 110 °C and 1 bar overpressure of CO for 3 hours, obtaining excellent yields. We reproduced the reaction employing 1,1-diphenyl-2-nitroethene (**1b**) (Scheme 4) as the substrate and obtained a very similar result (82% conversion and 92% indole selectivity in our hands, instead of 97% yield as reported, Table S2, entry 1).[15] However, the previously reported conditions appears to be suitable only for the very limited class of α-aryl-β-nitrostyrenes and when **1a** was employed as the substrate under the same experimental conditions, both conversion and selectivity were very poor (Table S2, entry 2, indole **2a** yield = 6.8%). Using our optimized conditions, excellent results were obtained with both substrates **1a** and **1b** (Table 1). The use of a different Pd(II) precursor ($Pd(OAc)_2$ or $[Pd(Phen)_2][BF_4]_2$) did not affect the system performance (Table S2, entries 4, 5).

The difference in reactivity between the two substrates **1a** and **1b** is due to two reasons: the higher reduction potential of β-substituted β-nitrostyrenes[16] with respect to β-nitrostyrene (**1i**), due to a tilting of the nitro group out the olefin plane, and the presence of a more extended π system in **1b**. In fact, since the nitro group reduction should involve an initial single-electron transfer from the metal to the nitroalkene with the formation of a radical anion,[17] (**A** in Scheme 5) a high conjugation degree of the π system should favor the radical delocalization and thus the subsequent formation of a nitroso compound (**B**), which is proposed to be the aminating species, by analogy with what it happens in the cyclization of *o*-nitrostyrenes.[18] Eventually the hydroxyindole (**C**), formed by animation, is reduced to the indole by carbon monoxide. The formation of the radical anion allows for an easy rotation around the double bond and explains why good selectivities in indole could be obtained even employing *trans*-β-nitrostyrenes that are selectively formed by the Henry reaction. The presence of a second aryl group in **1b** is expected to favor even the cyclization step because it maximizes the chances of a proper orientation of the nitroso and phenyl groups, in accord with the observation that **1b** gave the highest selectivity among all tested nitrostyrenes (*vide supra*).



Scheme 5. Proposed reaction mechanism

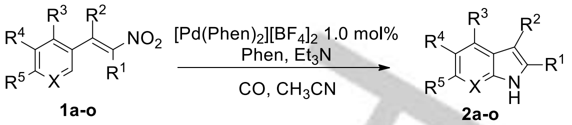
The scope of the reaction was then explored (Table 1). The best results were obtained for substrate **1b** due to the presence of the phenyl ring, as mentioned above. For other substrates lacking an aryl group in the *alpha* position, the presence of a substituent in the *beta* position was fundamental for the indole formation and its absence (**1i**) resulted in a low reactivity and palladium black formation. In this case, an insoluble solid derived from the polymerization of the starting β-nitrostyrene[19] was found as the main product of the reaction while 3,4-diphenylpyrrole was detected by GC-MS as the major product in solution. Both electron-withdrawing and electron-donating substituents can be present in the *para* position of the aryl ring. However, as expected, the presence of strongly electron-releasing groups, such as methoxide (**1f**) and even more diethylamino (**1k**), led to a reduced reactivity due to a slower reduction of the nitro group.[10c]

It is especially worth of note that good results were obtained with substrate **1e**. Indeed, azaindoles are very important molecules.[20] The cyclization of the nitroso intermediate is an electrophilic cyclization and the attack on the electron poor position 2 or 4 of the pyridine ring should be disfavored. The 80% regioselectivity in 2-methyl-1*H*-pyrrolo[2,3-b]pyridine, **2e**, the most disfavored product from an electronic point of view, may be ascribed to a partial coordination of the substrate to the metal center. On the contrary, the reductive cyclization of the chloro derivative **1h** is not regioselective.

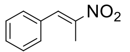
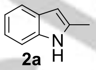
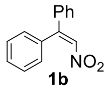
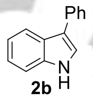
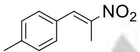
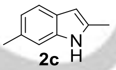
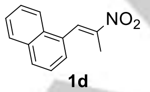
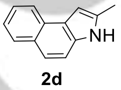
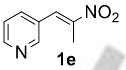
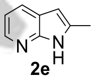
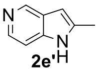
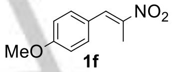
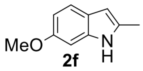
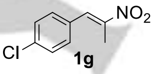
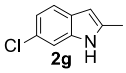
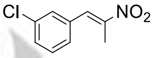
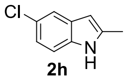
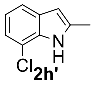
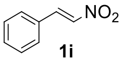
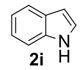
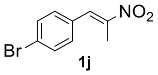
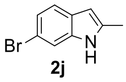
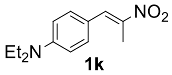
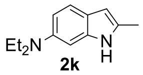
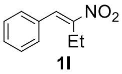
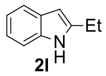
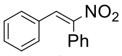
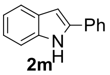
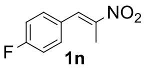
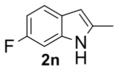
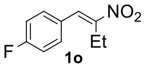
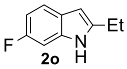
The reaction enables to synthesize a wide range of indoles from easily accessible and often commercially available aldehydes and nitroalkanes.

Since nitroalkanes are much more difficult to reduce than nitroalkenes, it is conceivable to run the Henry condensation and the following cyclization in one pot. Preliminary results show that this is indeed the case, but selectivities were poor because of the difficulty in finding a solvent mixture that is suitable for both the Henry condensation and the following cyclization. Further efforts will be done in this direction in the future.

Table 1. Scope of the reaction.



1a-o **2a-o**

Substrate	Product	Conv. (%)[b]	Yield (%)[c]
 **1a**	 **2a**	100	86
 **1b**	 **2b**	100	93
 **1c**	 **2c**	>99	70
 **1d**	 **2d**	>99	75
 **1e**	 **2e**	95	50
	 **2e'**		11[d]
 **1f**	 **2f**	94	59
 **1g**	 **2g**	100	51
 **1h**	 **2h**	100	21
	 **2h'**		20
 **1i**	 **2i**	64	3[b]
 **1j**	 **2j**	100	50
 **1k**	 **2k**	16	-
 **1l**	 **2l**	96	47
 **1m**	 **2m**	93	41
 **1n**	 **2n**	100	57
 **1o**	 **2o**	100	61

[a] Experimental conditions: [Pd(Phen)$_2$][BF$_4$]$_2$ = 1.10×10^{-2} mmol, mol ratio substrate/Phen/[Pd(Phen)$_2$][BF$_4$]$_2$ = 100:16:1, at 150 °C and 20 bar of CO, [Et$_3$N] = 0.17 M, in CH$_3$CN (15 mL), for 2.5 h. [b] Determined by GC analysis. [c] Isolated yield. [d] Determined by ^{1}H NMR using anisole as an internal standard.

Acknowledgements

We acknowledge the MiUR for financial support. One of us (F.F.) thanks the University of Milano for a postdoctoral fellowship.

Keywords: C-H activation; carbonylation; nitroalkenes; nitrogen heterocycles; palladium

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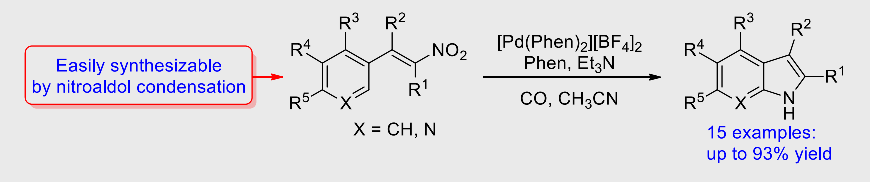

Indoles and azaindoles can be obtained by reductive cyclization of β-nitrostyrenes, which can be easily obtained in most cases from cheap nitroalkanes and aromatic aldehydes. The method is effective for the synthesis of both 2 and 3 substituted indoles.

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Synthesis of Indoles by Palladium-Catalyzed Reductive Cyclization of β-Nitrostyrenes with Carbon Monoxide as the Reductant.