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Synthesis of Indoles by Palladium-Catalyzed Reductive Cyclization of β-Nitrostyrenes with Phenyl Formate as a CO Surrogate

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Abstract: The reductive cyclization of suitably substituted organic nitro compounds by carbon monoxide is a very appealing technique for the synthesis of heterocycles because of its atom efficiency and easiness of separation of the only stoichiometric byproduct CO_2, but the need for pressurized CO has hampered its diffusion. We have recently reported on the synthesis of indoles by reductive cyclization of *o*-nitrostyrenes using phenyl formate as a CO surrogate, using a palladium/1,10-phenanthroline complex as catalyst. However, depending on the desired substituents on the structure, the use of β-nitrostyrenes as alternative reagents may be advantageous. We report here the results of our study on the possibility to use phenyl formate as a CO surrogate in the synthesis of indoles by reductive cyclization of β-nitrostyrenes, using $PdCl_2(CH_3CN)_2$ + phenanthroline as the catalyst. It turned out that good results can be obtained when the starting nitrostyrene bears an aryl substituent in the alpha position. However, when no such substituent is present, only fair yield of indole can be obtained because the base required to decompose the formate also catalyzes an oligo-polymerization of the starting styrene. The reaction can be performed in a single glass pressure tube, a cheap and easily available piece of equipment.

Keywords: indoles; nitrostyrenes; cyclization; reduction; carbon monoxide; CO surrogates: palladium; homogeneous catalysis; nitrogen ligands

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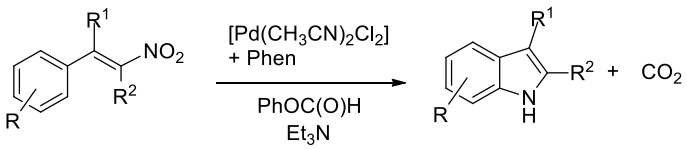
1. Introduction

Indoles represents one of the most important classes of nitrogen heterocycles and many methods have been published for their synthesis [1–5]. Yet, many of the reported procedures employ large amounts of expensive or toxic reagents, whose excess or byproducts may be difficult to remove at the end of the reaction. Among the classes of reactions that can be employed to produce nitrogen heterocycles, reductive cyclization of organic nitro compounds by carbon monoxide is one of the most appealing from this point of view, because only CO_2 is formed as a stoichiometric byproduct and the excess of reducing agent is easily removed with the produced CO_2 simply upon venting the autoclave [6–12]. Despite these apparent advantages, the use of carbon monoxide as a reducing agent has not spread outside the limited number of groups that have developed these reactions, the reason likely being connected with the difficulty in handling pressurized CO and with the required safety measurements. The latter problem is also common to other reactions employing pressurized CO and, in order to circumvent it, the field of so-called CO surrogates has been intensely developed in the last decade. The latter are solid or liquid molecules able to liberate CO during the reaction under either a thermal stimulus or the action of a second reagent, typically a base. The use of CO surrogates has already been reviewed several times [13–17].

In the field of reductive cyclization of nitro compounds, we first introduced the use of formate esters for the reductive cyclization of *o*-nitrostyrenes to indoles a few years ago [18,19]. Both alkyl- and aryl-formates could be used as CO surrogates, but the latter allowed to obtain higher selectivities and to work under milder conditions. We later extended the use of aryl formates as CO surrogates even to the synthesis of 3,6-dihydro-2*H*-[1,2]-oxazines from nitroarenes and conjugated dienes [20] and the application to the reductive cyclization of *o*-nitrobiaryls to carbazoles has also been developed [21]. Notably, reaction yields higher than those obtainable by the use of gaseous CO were achieved in many cases. A related triformate, benzene-1,3.5-triyl triformate, has also been employed by Wu and coworkers for two reactions in this field: the carbonylation of *o*-nitroanilines to give benzimidazolones [22] and the *inter*-molecular carbonylation of *o*-nitrobenzyl halides with amines to give 3,4-dihydroquinazolin-2(1*H*)-ones [23].

Most of the reported reactions for the synthesis of *N*-heterocycles starting from organic nitro compounds and CO as the reductant employ suitably substituted *o*-nitroarenes as substrates [24–31], although examples of inter-molecular reactions of nitroarenes have also been reported [32–34]. Much less attention has been paid to the use of nitroalkenes as substrates. Dong was the first to report the use of α-aryl-β-nitrostyrenes as substrates for the synthesis of indoles by reductive cyclization using CO as the reductant [35]. We later extended the range of suitable substrates for the same reaction [36] and also applied as substrates β-nitrothiophenes, to give thienopyrroles [37], and nitrodienes, to give pyrroles [38]. The use of formates as CO surrogates in combination with nitroalkenes has not been reported yet, with the exception of a single experiment under unoptimized conditions described in our first communication on the subject [19]. However, it should be mentioned that $Mo(CO)_6$ has been previously employed to this aim [39] and that a single example of a cyclization of this kind employing CO_2+$(Ph_2MeSi)_2$ has also been reported [40]. In this paper, we describe our studies on the reductive cyclization of β-nitrostyrenes by phenyl formate as a CO surrogate (Scheme 1).



Scheme 1. Synthesis of indoles from β-nitrostyrenes with PhOC(O)H as a CO surrogate.

The catalyst employed is an in situ formed complex of palladium with 1,10-phenanthroline (Phen) as ligand. This kind of complexes have proved to be the most active and robust catalysts for reactions involving the reduction of organic nitro compounds not only in the field of cyclization reactions [24,33,41–44], but also in the field of the synthesis of base chemicals such as carbamates and ureas [45–52], where very high turnover numbers are required to make the catalyst economically appealing.

2. Results and Discussion

Optimization of the Reaction Conditions

The only previously reported data on the use of formate esters as CO surrogates for the reductive cyclization of a nitroalkene refers to a single preliminary test on the cyclization of β-methyl-β-nitrostyrene (R = R^1 = H, R^2 = CH_3 in Scheme 1) employing $PdCl_2(CH_3CN)_2$/Phen as catalyst, in CH_3CN as solvent and with phenyl formate as the CO surrogate [18]. Triethylamine was employed as the base necessary to catalyze the decomposition of phenyl formate to CO and phenol. We first reproduced this experiment (Table 1, entry 1), obtaining similar results (39% selectivity and 80% conversion vs. 41% selectivity and 100% conversion). The small difference is attributable to the different experimental apparatus employed in the two cases (see experimental). Starting from this point, we changed a series of parameters. The main results are here briefly described.

Table 1. Optimization of the reaction conditions for the reductive cyclization of β-methyl-β-nitrostyrene (**1a**) to 2-methylindole (**2a**) [1].

Entry	Phen (mol%)	T (°C)	Base	Base Amount (mmol)	Solvent	Conv.% [2]	Select.% [3]
1	2.5	140	Et_3N	0.29	CH_3CN	80	39
2	10	140	Et_3N	2.30	CH_3CN	>99	40
3	10	140	Et_3N	2.30	THF	85	30
4	10	140	Et_3N	2.30	DMF	>99	41
5	10	140	Et_3N	2.30	$C_6H_5CH_3$	52	12
6	10	140	Et_3N	2.30	CH_3OH	85	9
7 [4]	10	140	-	-	CH_3CN	~0	0
8 [5]	10	140	Et_3N	2.30	CH_3CN	61	0
9	10	120	Et_3N	0.29	CH_3CN	32	31
10	10	120	Py	0.29	CH_3CN	<1	<1
11	10	150	Py	0.29	CH_3CN	17	18
12	10	120	NaOAc	0.29	CH_3CN	62	17
13	10	120	Na_3PO_4	0.29	CH_3CN	78	7
14 [6]	10	140	Et_3N	2.30	CH_3CN	>99	26
15 [6]	10	140	Et_3N	0.29	CH_3CN	95	28
16 [7]	10	140	Et_3N	2.30	CH_3CN	>99	47

[1] Experimental conditions: 0.54 mmol **1a**, 1 mol % $PdCl_2(CH_3CN)_2$, 260 μL (2.38 mmol) phenyl formate, in 10 mL of the indicated solvent, for 7 h; other amounts and conditions as in the table. 0.29 mmol Et_3N corresponds to 40 μL; Py = pyridine. [2] Conversion calculated with respect to starting **1a**. [3] Selectivity in **2a** calculated with respect to reacted **1a**. [4] No phenyl formate and no base were added. [5] No phenyl formate was added. [6] 5 mol % $PdCl_2(CH_3CN)_2$. [7] 350 μL phenyl formate.

A few explorative tests led to the conclusion that a larger amount of phenanthroline and base afforded a more active and stable catalytic system, even though the selectivity in indole was not improved (Table 2, entry 2). The only other tested solvent (entries 2–6) that gave results comparable to acetonitrile was DMF. However, the latter is a more toxic and less easy to separate from the reaction products than CH_3CN and we decided not to employ it.

In order to understand the reasons for the failure in reaching selectivities comparable with those previously obtained for the same reaction by the use of gaseous CO [36], we investigated the stability of the starting β-nitrostyrene under the reaction conditions and in the presence of only some of the reagents. No reaction was observed under typical reaction conditions in the absence of phenyl formate when only the palladium catalyst and phenanthroline were added (entry 7). However, when the base was also added in the absence of any formate, a significant 61% consumption of β-nitrostyrene was observed. A very small amount of benzaldehyde, the product of a retro-Henry hydrolysis of the reagent, was observed by GC and ^{1}H NMR. No other decomposition product could be observed by GC analysis, suggesting that they are oligomeric or polymeric species. β-Nitrostyrenes are known to be prone to polymerization by a base-catalyzed process [53]. Clearly, a competition is occurring between the cyclization and the decomposition reaction, with the base accelerating both.

Bases different from Et_3N could promote the reaction to different extent, but they apparently also promoted the alternative decomposition pathways and the selectivities in indole were always lower (entries 9–13). Increasing the catalyst amount to 5 mol% did not solve the problem (entries 14, 15).

At this stage, it is instructive to recall that when gaseous CO was employed as the reductant for the reductive cyclization of β-substituted-β-nitrostyrenes, high selectivities were only observed at CO pressures higher than 20 bar (measured at RT) [36]. Retrospectively, these relatively high pressures are likely needed to speed-up the reduction reaction with respect to the polymerization, which is likely insensitive to the CO pressure. Indeed, the only attempt in which the selectivity in indole could be improved was that performed employing a larger amount of formate (entry 16). However, working with such a large amount of formate is unsafe because in the worst-case scenario, complete decomposition

of the formate and no CO consumption, the total pressure inside the reaction vessel at the reaction temperature would exceed 10 bar, which is considered as the safety pressure limit of glass pressure tubes. Thus, we decided not to pursue this strategy any more. Although the problem may be solved by performing the reaction in a steel autoclave, this was not the aim of the present work. The key role of a high CO pressure is also evidenced by the failure to increase the selectivity of the reaction by increasing the catalyst amount at a fixed formate concentration.

Table 2. Optimization of the reaction conditions for the reductive cyclization of α-phenyl-β-nitrostyrene (**1b**) to 3-phenylindole (**2b**) [1].

Entry	Pd (mol%)	Phen (mol%)	T (°C)	t (h)	Et_3N (μL)	PhOC(O)H (μL)	Conv.% [2]	Select.% [3]
1	1	5	110	3	120	260	>99	84
2	1	5	120	3	120	260	>99	87
3	1	5	130	3	120	260	>99	90
4	1	5	140	3	120	260	>99	92
5	1	5	150	3	120	260	>99	77
6	1	5	140	3	20	260	>99	84
7	1	5	140	3	40	260	>99	85
8	1	5	140	3	60	260	>99	87
9	1	5	140	3	80	260	>99	88
10	1	5	140	3	120	200	97	81
11	1	5	140	3	120	350	>99	91
12	1	5	140	3	200	350	>99	90
13	1	2.5	140	3	120	260	94	85
14	1	2.5	140	3	80	260	>99	83
15	1	2.5	140	7	40	260	>99	87
16	1	2.5	140	16	40	260	>99	87
17	1	10	140	3	120	260	>99	90
18	0.5	5	140	3	120	260	>99	78
19	0.5	5	140	6	120	260	>99	79
20 [4]	2	5	140	3	120	260	>99	90
21 [4]	2	5	140	1.5	120	260	>99	90
22 [5]	1	5	140	3	120	260	>99	88
23 [6]	1	5	140	3	120	260	>99	85

[1] 0.54 mmol **1b**, in 10 mL CH_3CN; other amounts and conditions as in the table. [2] Conversion calculated with respect to starting **1b**. [3] Selectivity in **2b** calculated with respect to reacted **1b**. [4] Pd-black precipitation was observed after 1 h reaction. [5] In DMF (10 mL) as solvent. [6] In CH_3CN + DMF (9 + 1 mL) as solvent.

Since the reductive cyclization of α-aryl-β-nitrostyrenes is faster than that of β-substituted-β-nitrostyrenes [35,36] we then moved to optimizing the reaction conditions for α-phenyl-β-nitrostyrene (**1b,** R = R^2 = H, R^1 = Ph in Scheme 1), also taking into consideration the results described above.

The reaction temperature was first optimized (Table 2, entries 1–5, and Figure 1). As expected, based on the reactivity observed under CO pressure, the reaction can be performed even at 110 °C. However, the selectivity in the formation of the desired indole increases up to 140 °C, after which a drop is observed.

The effect of the amount of base is moderate, but an almost linear increase in the selectivity is observed at 140 °C on passing from 20 to 120 μL of Et_3N (Entries 4, 6–9 and Figure 2).

Decreasing the phenyl formate amount (Entry 10 vs. entry 4) led to an incomplete conversion of the reagent and a lower selectivity in indole, which is not surprising. However, contrary to what observed in the case of **1a**, even increasing the formate amount (entry 11) did not improve the selectivity. The difference between the two substrates is likely because whereas the reductive carbonylation of **1a** requires pressures in excess of 20 bar to selectively afford **2a**, the corresponding reaction of **1b** can be successfully performed at much lower pressures [35]. Thus, a larger excess of formate is not needed. By working at the larger formate amount, the effect of a larger amount of base was also tested (entry 12), but

no improvement was observed, indicating that 120 μL of Et_3N is the best base amount to be added.

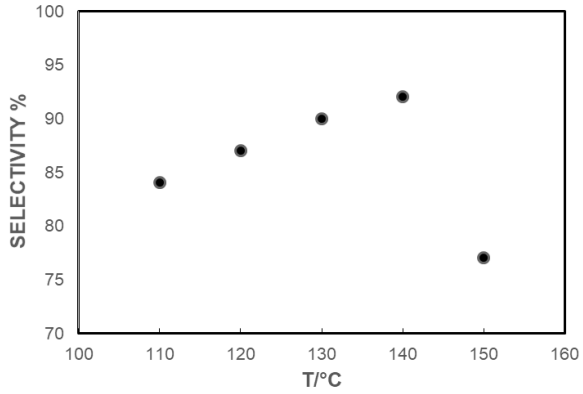


Figure 1. Optimization of the reaction temperature for the reductive cyclization of α-phenyl-β-nitrostyrene (**1b**) to 2-phenylindole (**2b**). Data from Table 2.

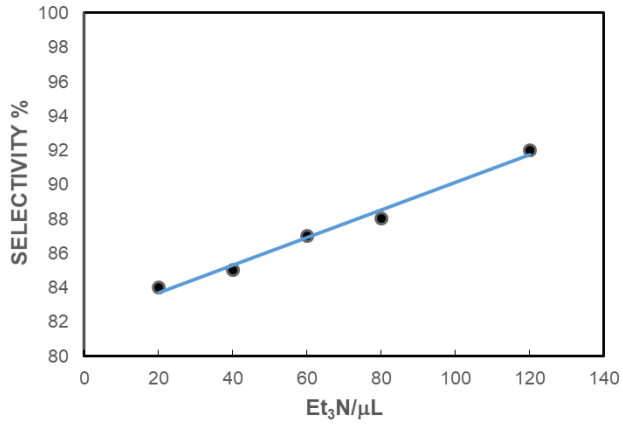


Figure 2. Optimization of the Et_3N amount for the reductive cyclization of α-phenyl-β-nitrostyrene (**1b**) to 2-phenylindole (**2b**). Data from Table 2.

Halving the amount of phenanthroline (entry 13) led to a less stable catalytic system, but doubling it (entry 17) did not lead to any improvement. At the lowest ligand amount, the effect of a different base concentration and reaction time was also investigated. In particular, a longer reaction time does not alter the selectivity of the reaction (entries 15, 16). This on one side means that **2b** is stable under the reaction conditions; on the other hand the lower selectivity with respect to the ideal conditions is not due to the accumulation of a long-lived intermediate, for example the *N*-hydroxyindole, which only more slowly converts to the final product.

Halving the amount of catalyst decreases the selectivity, an effect that cannot be counterbalanced by an increased reaction time (entries 18, 19). On the other hand, when the amount of catalyst was doubled, the reaction accelerated and was complete in less than one hour (entries 20, 21) as evidenced by the formation of palladium black on the walls of the reaction tube, but the selectivity was even decreased with respect to that achievable by working at a 1 mol% catalyst amount. Though the decrease in selectivity is not easily explained, the early formation of palladium black is a consequence of the reaction ending in a short time. Indeed, during the reaction the oxidation state of palladium shuttles between zero and two, but zerovalent palladium complexes with nitrogen ligands are not stable under a CO atmosphere. Thus, if some nitro compound is present that can oxidize back palladium(0) to palladium(II) at a rate faster than decomposition, the reaction can proceed, but if no oxidizing compound is any longer present, then aggregation of the accumulated

Pd(0) species results in the bulk metal formation. This behavior is quite standard for palladium-catalyzed carbonylation reactions of nitro organic compounds of any kind.

While this work was in progress, a parallel work in our laboratories evidenced that the use of a CH_3CN/DMF (9:1) solvent mixture afforded better results than any of the two solvents separately in the reductive cyclization of *o*-nitrostyrenes to indoles, a reaction with many similarities to that investigated here [18]. We thus tested if the same positive effect could be observed for β-nitrostyrenes, but both the use of neat DMF and that of the CH_3CN/DMF mixture led to a lower indole selectivity (entries 22, 23).

With the optimized conditions in our hands, we investigated the reaction scope of the cyclization (Table 3). The only difference with respect to the optimized conditions was that the reaction time was increased from three to four hours. This was made to maximize chances that substrates less reactive than **1b** could anyway reach a complete consumption in the allowed time.

Table 3. Substrate scope [1].

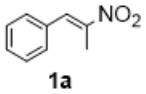
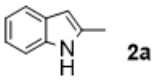
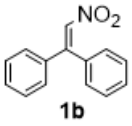
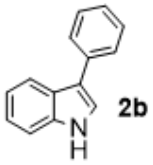
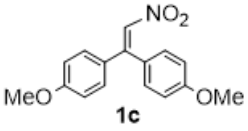
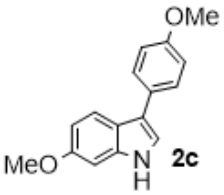
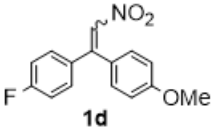
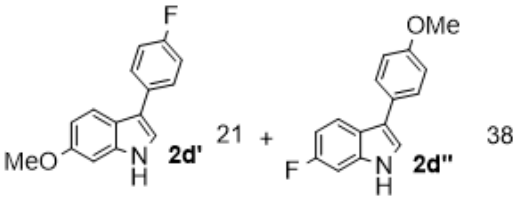
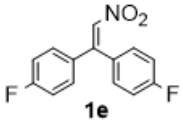
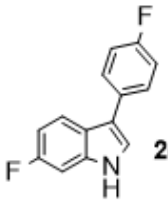
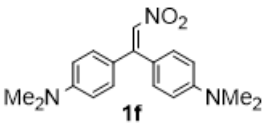
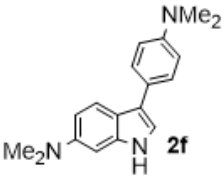
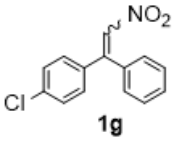
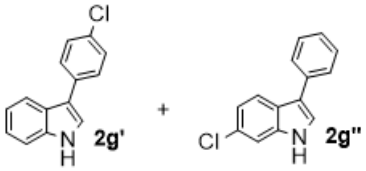
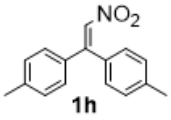
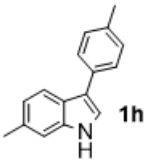
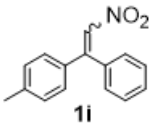
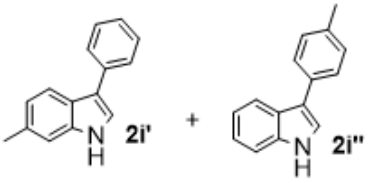
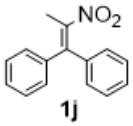
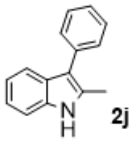
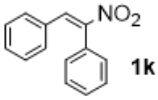
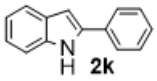
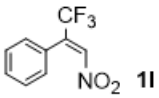
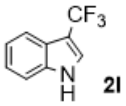
Entry	Substrate	Product	Yield [2]
1 [3]	 **1a**	 **2a**	43(47) [4]
2	 **1b**	 **2b**	89(92) [4]
3	 **1c**	 **2c**	66
4	 **1d**	 **2d'** 21 + **2d''** 38	
5	 **1e**	 **2e**	49
6	 **1f**	 **2f**	_ [5]

Table 3. *Cont.*

Entry	Substrate	Product	Yield [2]
7	 **1g**	 **2g'** + **2g''**	67(1:2.5)
8	 **1h**	 **1h**	70
9	 **1i**	 **2i'** + **2i''**	71(1.3:1)
10	 **1j**	 **2j**	47
11	 **1k**	 **2k**	(34) [4]
12	 **1l**	 **2l**	_ [5]

[1] Experimental conditions: 0.54 mmol **1**, 1 mol % $PdCl_2(CH_3CN)_2$, 5 mol % Phen, 260 μL PhOC(O)H, 120 μL Et_3N, 140 °C for 4 h, in 10 mL CH_3CN. [2] Isolated yields. [3] Experimental conditions: 0.54 mmol **1**, 1 mol % $PdCl_2(CH_3CN)_2$, 10 mol % Phen, 350 μL PhOC(O)H, 320 μL Et_3N, 140 °C for 7 h, in 10 mL CH_3CN. [4] GC yield in parenthesis. [5] No product could be isolated.

Before discussing the individual results, it is worth recalling that the initial reduction of the nitro compound has been shown to be an electron transfer from the metal complex to the nitro compound in all of the cases in which this step has been investigated in detail [54–65]. As a consequence, the presence of electron withdrawing groups close to the nitro group accelerates the reaction and that of electron donating groups slows it down. In the present case, it should also be considered that alkenes bearing electron withdrawing groups can coordinate to zerovalent palladium complexes and, specifically, coordination of nitrostyrenes to the Pd^0(2,9-Me_2-4,7-Ph_2-Phen) moiety has been experimentally proofed [66]. Coordination to the corresponding moiety with unsubstituted phenanthroline should be even stronger. However, this coordination may have both positive (catalyst stabilization) and negative (catalyst deactivation) effects and these are difficult to analyze without an extensive series of kinetic data. Thus, we will only discuss the former type of contribution. A more comprehensive discussion of the effect of different parameters on reductive carbonylation/cyclization of organic nitro compounds has been reported in a recent review [10] and we address the interested reader to that for more information.

With respect to the substituent on the aryl rings of α-aryl-β-nitrostyrenes, both electron withdrawing groups (F, Cl. Table 3, entries 5, 7) and donating (Me, MeO, entries 3, 8) are well tolerated. The only exception is represented by the very strongly electron donating group dimethylamino (entry 6). This group is often incompatible with this kind of reactions

and had also failed to give the desired product when $Mo(CO)_6$ had been used as a CO surrogate [39]. The result is not surprising given what said above concerning the nitro compound activation.

An interesting aspect from the synthetic point of view is the possibility of having a regioselective reaction when two different aryl rings are present in the substrate. It should be recalled that rotation around the central C=C bond is clearly easy under the reaction conditions (see later for the reason). Indeed, β-alkyl-β-nitrostyrenes cyclize without problems, both when the reaction is performed under a CO pressure [36,37] and when in the presence of $Mo(CO)_6$ [39], despite the fact that they are prepared by a Henry condensation that selectively affords the compound with the nitro and aryl groups in the *trans* position. Despite the lower efficiency of the procedure used in this work for this kind of substrates, the same conclusion clearly apply to the experimental conditions here employed. From a general point of view, the cyclization step should be an aromatic electrophilic substitution reaction and be easier on an electron rich ring. In the previous literature, there is only one example relevant to this point. Cyclization of *(E)*-3-(2-nitropropenyl)thiophene, where a phenyl and a thiophene rings are in competition, afforded a mixture of products with a 55/40 prevalence of that deriving from the functionalization of the electron rich thiophene ring despite the fact that in the reagent the nitro group was selectively oriented towards the phenyl ring [37].

In this work, the possible selectivity of the reaction with respect to the preferentially reacting ring was tested by putting in competition the couples 4-fluorophenyl-4-methoxyphenyl, chlorophenyl-phenyl, methyl-phenyl (entries 4, 7, 9). However, only a moderate regioselectivity was observed and a preferential functionalization of the most electron rich ring was observed only in one out of three cases. The obtained regioselectivity does neither match the initial *cis-trans* ratio in the starting nitroalkenes. This indicates a more complex reaction mechanism, possibly involving an active role by the metal. However, data are at the moment insufficient to draw any general conclusion and a dedicated mechanistic study should be performed to give a final answer to this point.

The reaction is compatible with the presence of both a phenyl ring in the *alpha* position and methyl group in the *beta* position of the styrene (entry 10). The better result with respect to that achievable in the absence of the α-phenyl substituent (entry 1) is further evidence that electronic delocalization effects on both aryl rings of the substrate are the reason for the better results obtainable when an α-aryl ring is present. The position of the aryl ring is important and moving it from the *alpha* to the *beta* position led to much worse results (entries 2, 11).

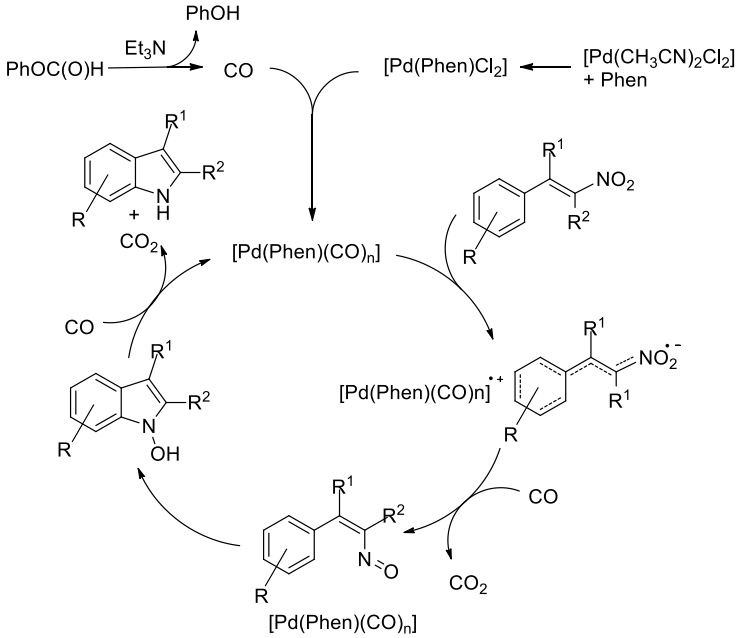
Given the importance of trifluoromethyl groups in pharmaceutical chemistry, we also synthesized α-trifluoromethyl-β-nitrostyrene (1k). However, no indole could be isolated from the corresponding cyclization reaction (entry 12).

Although no specific mechanistic study was made during this study, the obtained results are fully consistent with a scenario analogous to those identified for other related reactions (Scheme 2).

Initially, the active catalyst is generated by coordination of phenanthroline to palladium, followed by reduction of palladium(II) to palladium(0) by the CO liberated by the decomposition of phenyl formate. The so formed complex is able to activate the nitrostyrene by an electron transfer. At this stage, rotation around the weakened C=C double bond can occur. We have previously suggested such possibility based on general orbital considerations [36–38], however, we recently became aware that *trans-cis* isomerization of β-nitrostyrenes has indeed been experimentally observed upon generation of the corresponding radical anion [67]. This older report supports the validity of our proposal.

Collapse of the radical couple results in the reduction of the nitro group to nitroso. Electrophilic attack of the nitroso group on the arene then affords a hydroxyindole. It is not certain if this step occurs outside the coordination sphere of the metal or if palladium accelerates it. Hydroxyindoles have been observed or even isolated in related reactions [10].

Reduction of the latter by the palladium-carbonyl complex eventually liberates the final indole with regeneration of the active catalyst.



Scheme 2. Proposed reaction mechanism.

3. Materials and Methods

3.1. General Procedures

All reactions and manipulations were performed under a dinitrogen atmosphere using standard Schlenk apparatus, unless otherwise specified. All glassware and magnetic stirring bars were kept in an oven at 120 °C for at least two hours and let to cool under vacuum before use. Et_3N and CH_3CN were dried by distillation from CaH_2. DMF was dried by distillation over CaH_2, under reduced pressure at 60 °C. Dried solvents were stored under a dinitrogen atmosphere. Phenyl formate was prepared following a procedure reported in the literature [68]. Deuterated solvents were purchased from Sigma-Aldrich: $CDCl_3$ was filtered on basic alumina and stored under dinitrogen over 4 Å molecular sieves. 1,10-Phenanthroline (Phen) was purchased as hydrate (TCI Europe NV). It was dissolved in CH_2Cl_2, dried over Na_2SO_4 followed by filtration under a dinitrogen atmosphere and evaporation of the solvent in vacuo. Phen was weighed in the air but stored under dinitrogen to avoid water uptake. $Pd(CH_3CN)Cl_2$ was prepared starting from commercially available $PdCl_2$ following a procedure reported in the literature [69]. All other reagents were purchased from Merck (Sigma-Aldrich), TCI Europe NV or Fluorochem and used without further purifications. The starting β-nitrostyrenes were prepared by methods reported in the literature [39,70,71]. Details are reported in the Supplementary Materials. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a *Bruker Avance DRX 300*, *Bruker Avance DRX 400* or *Avance NEO 400*. Chemical shifts are reported in ppm relative to TMS. Gas-chromatographic analyses were performed using a *Shimadzu* 2010Pro gas chromatograph equipped with a Supelco SLB^{TM}-5 ms capillary column (L × I.D. 10 m × 0.10 mm, df 0.10 μm). A standard analysis involves the preparation of a sample solution in CH_2Cl_2 (conc. 0.3 mg/mL calculated with respect to naphthalene used as the internal standard). Elemental analyses were performed on a *Perkin Elmer 2400 CHN* elemental analyzer.

3.2. Apparatus

We have discussed in depth the different kind of pressure tubes that can be employed and the corresponding advantages and disadvantages in a very recent paper [18] and we refer to that paper for a more complete discussion. In the present work, we employed

23 mL Duran heavy walls (2.5 mm) borosilicate glass tubes with Schott PTB screw caps completed with PTFE protected seals, both commercialized by Fisher Scientific (Figure S1 left, Supplementary Materials), and heated them in a custom-made aluminum block placed on a magnetic stirring and heating plate (Figure S1 right). An oil bath can be alternatively used. CAUTION: Although we never had problems with the pressure tubes over several hundred reactions, the tubes must always be checked for scratches or cracks that may result in a reduced resistance to pressure and the possibility that an explosion occurs should always be considered. Reactions must be performed in a well-ventilated hood and with the use of a protective shield.

3.3. General Methods for Catalytic Reactions

To avoid weighing too small amount of substance, stock solutions of Pd catalyst and Phen were separately prepared under dinitrogen in CH_3CN. For a typical catalytic reaction, a pressure tube (see the Apparatus section) equipped with a magnetic stirring bar was charged with the nitrostyrene (0.54 mmol). The tube was placed in a large mouth Schlenk tube and evacuated and filled with dinitrogen three times. The appropriate volume of stock solutions of the catalysts and Phen were added and the mixture stirred for 10 min, to allow the formation of Pd/Phen complex. Precipitation of $Pd(Phen)Cl_2$ may be observed depending on the catalyst concentration The solvent (total solvent amount was 10 mL), HCOOPh and the base were added in this order and the pressure tube sealed under nitrogen. The tube was then placed in a custom-made aluminum block preheated at the desired temperature and heated while stirring for the required time. Detailed experimental conditions are reported in the captions to the tables.

At the end of the reaction, the pressure tube was lifted from the heating block, let to cool to room temperature and opened (Attention: residual CO pressure is present in the pressure tube, perform the operation slowly under a hood). When quantitative GC analysis of the reaction was needed, naphthalene was then added to the reaction mixture as the internal standard, the reaction stirred until its complete solubilization and then the reaction mixture immediately analyzed. Otherwise, the solvent was evaporated and the residue subjected to column chromatography (silica gel) using hexane/AcOEt as the eluent with the addition of 1 to 2% of Et_3N to partially deactivate acidic sites of silica gel. In our experience, absence of Et_3N causes extensive decomposition of the indoles over silica-gel.

3.4. Characterization Data for Indoles

2-Methyl-1*H*-indole (2a). Obtained as a white solid (31 mg, 0.23 mmol, 43% yield) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (br s, 1H, N*H*), 7.51 (d, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.15–6.99 (m, 2H), 6.22 (s, 1H), 2.43 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1 (*C*), 135.7 (*C*), 129.1 (*C*), 120.9 (*C*H), 119. 7 (*C*H), 110.4 (*C*H), 100.3 (*C*H), 13.5 (CH_3). Elemental Analysis for C_9H_9N Calcd.: C, 82.41; H, 6.92; N, 10.48%. Found: C, 82.12; H, 6.98; N, 10.30%.

3-Phenyl-1*H*-indole (2b). Obtained as a white solid (93 mg, 0.48 mmol, 89% yield) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N). ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.3 Hz, 2H), 7.52–7.44 (m, 3H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.35–7.26 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8 (*C*), 135.7 (*C*), 128.9 (*C*H), 127.7 (*C*H), 126.1 (*C*H), 125.9 (*C*), 122.6 (*C*H), 121.9 (*C*H), 120.5 (*C*H), 120.0 (*C*H), 118.5 (*C*), 111.5 (*C*H) ppm. Elemental Analysis for $C_{14}H_{11}N$ Calcd.: C, 87.01; H, 5.74; N, 7.25%. Found: C, 86.90; H, 5.84; N, 7.01%.

6-methoxy-3-(4-methoxyphenyl)-1*H*-indole (2c). Obtained as a white solid (92 mg, 0.36 mmol, 66% yield) after column chromatography (hexane:AcOEt = 80:20 to 60:40 + 1% Et_3N);. ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (br, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 2.2 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.1 Hz, 1H), 3.87 (s, 3H), 3.86 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2 (*C*), 156.8 (*C*), 137.5 (*C*), 128.6 (*C*H), 128.3 (*C*), 120.6 (*C*H), 120.5 (*C*), 119.9 (*C*H), 118.1 (*C*), 114.4 (*C*H), 110.2

(*C*H), 94.8 (*C*H), 55.8 (OCH_3), 55.5 ppm (OCH_3). Elemental Analysis for $C_{16}H_{15}NO_2$ Calcd.: C, 75.87; H, 5.97; N, 5.53%. Found: C, 75.90; H, 6.14; N,5.81%.

3-(4-fluorophenyl)-6-methoxy-1*H*-indole (2d′). Obtained as a white solid (27 mg, 0.21 mmol, 21% yield) after column chromatography (hexane:AcOEt = 85:15 + 1% Et_3N); 21% yield ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.65–7.54 (m, 2H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.16–7.09 (m, 2H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 8.7, 2.2 Hz, 1H), 3.87 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5 (d, $^1J_{C\text{-}F}$ = 244.4 Hz, *C*F), 156.8 (*C*OCH$_3$), 137.6 (*C*), 131.8 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, *C*), 128.8 (d,$^3J_{C\text{-}F}$ = 7.7 Hz, *C*H), 120.5 (*C*H), 120.3 (*C*H), 120.2 (*C*), 117.4 (*C*), 115.7 (d, $^2J_{C\text{-}F}$ = 21.3 Hz, *C*H), 110.5 (*C*H), 94.9 (*C*H), 55.8 (OCH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -117.37 ppm. Elemental Analysis for $C_{15}H_{12}FNO$ Calcd.: C, 74.67; H, 5.01; N, 5.81%. Found: C, 74.57; H, 5.21; N, 5.61%.

6-fluoro-3-(4-methoxyphenyl)-1*H*-indole (2d″). Obtained as a white solid (50 mg, 0.21 mmol, 38% yield) after column chromatography (hexane:AcOEt = 85:15 + 1% Et_3N). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.78 (dd, *J* = 8.8, 5.4 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 9.5, 2.3 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.94 (ddd, *J* = 9.4, 8.9, 2.3 Hz, 1H), 3.85 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5 (d, $^1J_{C\text{-}F}$ = 238.2 Hz, *C*F), 158.7 (*C*OCH$_3$), 136.9 (d, $^3J_{C\text{-}F}$ = 12.4 Hz, *C*), 129.0 (*C*H), 128.1 (*C*), 123.0 (*C*) 121.7 (d, $^3J_{C\text{-}F}$ = 3.3 Hz, *C*H), 121.0 (d, $^3J_{C\text{-}F}$ = 10.1 Hz, *C*H), 118.5 (*C*), 114.7 (*C*H), 109.3 (d, $^2J_{C\text{-}F}$ = 24.4 Hz, *C*H), 98.0 (d, $^2J_{C\text{-}F}$ = 26.0 Hz, *C*H), 55.8 (OCH_3) ppm. ^{19}F NMR (282 MHz, CD_2Cl_2) δ -121.17 ppm. Elemental Analysis for $C_{15}H_{12}FNO$ Calcd.: C, 74.67; H, 5.01; N, 5.81%. Found: C, 74.78; H, 5.31; N, 5.49%.

6-fluoro-3-(4-fluorophenyl)-1*H*-indole (2e). Obtained as an off-white solid (61 mg, 0.27 mmol, 49% yield) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.77 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.63–7.54 (m, 3H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.20–7.08 (m, 4H), 6.97 (td, *J* = 9.3, 2.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (d, $^1J_{C\text{-}F}$ = 244.9 Hz, *C*), 160.2 (d, $^1J_{C\text{-}F}$ = 238.6 Hz, *C*), 136.7 (d, $^3J_{C\text{-}F}$ = 12.4 Hz, *C*), 131.3 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, *C*), 129.0 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, *C*H), 122.5 (*C*), 121.9 (d, $^3J_{C\text{-}F}$ = 3.3 Hz, *C*H), 120.5 (d, $^3J_{C\text{-}F}$ = 10.1 Hz, *C*H), 117.7 (C), 115.8 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, *C*H), 109.28 (d, $^2J_{C\text{-}F}$ = 24.4 Hz, *C*H), 97.82 (d, $^2J_{C\text{-}F}$ = 26.0 Hz, *C*H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.84, -120.78 ppm. Elemental Analysis for $C_{14}H_9F_2N$ Calcd.: C, 73.36; H, 3.96; N, 6.11%. Found: C, 72.95; H, 4.27; N, 5.84%.

3-(4-chlorophenyl)-1*H*-indole (2g′) and **6-chloro-3-phenyl-1*H*-indole (2g″).** Obtained as an off-white solid (82 mg, 0.36 mmol, 67% yield) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H, N*H*, **2g′** isomer), 8.20 (s, 1H, N*H*, **2g″** isomer), 7.90 (d, *J* = 7.9 Hz, 1H, **2g′** isomer), 7.84 (d, *J* = 8.5 Hz, 1H, **2g″** isomer), 7.64 (d, *J* = 7.8 Hz, 2H, **2g″** isomer), 7.60 (d, *J* = 8.4 Hz, 2H, **2g′** isomer), 7.46 (t, *J* = 7.7 Hz, 2H, **2g″** isomer), 7.45–7.39 (m, 3H, **2g′** isomer and 1H, **2g″** isomer), 7.35–7.20 (m, 3H, **2g′** isomer and 2H, **2g″** isomer), 7.17 (dd, *J* = 8.6, 1.8 Hz, 1H, **2g″** isomer) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1 (*C*, **2g″**), 135.1 (*C*, **2g″**), 129.03 (*C*H, **2g′**), 128.99 (*C*H, **2g″**), 128.7 (CH, **2g′**),128.4 (*C*, **2g″**), 127.6 (*C*H, **2g″**), 126.4 (*C*H, **2g″**), 124.6 (*C*, **2g″**), 122.7 (*C*H, **2g′**),122.4 (*C*H, **2g″**), 122.0 (*C*H, **2g′**), 121.2 (*C*H, **2g″**), 120.7 (*C*H, **2g″**), 120.6 (*C*H, **2g′**), 119.7 (*C*H, **2g′**), 118. (*C*, **2g″**), 117.3 (*C*, **2g′**), 111.6 (*C*H, **2g′**),111.4 (*C*H, **2g″**) ppm. Elemental Analysis for $C_{14}H_{10}ClN$ Calcd.: C, 73.85; H, 4.43; N, 6.15%. Found: C, 74.15; H, 4.53; N, 5.84%.

6-methyl-3-(4-methylphenyl)-1*H*-indole (2h). Obtained as a white solid (83 mg, 0.38 mmol, 70% yield) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.27–7.25 (m, 3H, overlapped with $CDCl_3$), 7.21 (s, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 2.49 (s, 3H), 2.41 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3 (*C*), 135.6 (*C*), 132.9 (*C*), 132.3 (*C*), 129.6 (*C*H), 127.4 (*C*H), 123.9 (*C*), 122.1 (*C*H), 120.9 (*C*H), 119.7 (*C*H), 118.3 (*C*), 111.4 (*C*H), 21.8 (CH_3), 21.3 (CH_3) ppm. Elemental Analysis for $C_{16}H_{15}N$ Calcd.: C, 86.84; H, 6.83; N, 6.33%. Found: C, 87.10; H, 6.98; N, 6.02%.

6-methyl-3-phenyl-1*H*-indole (2i′) and **3-(4-methylphenyl)-1*H*-indole (2i″).** Obtained as a pale-yellow solid (78 mg, 0.38 mmol, 71% yield, mixture of the two isomers **2i**′ and **2i**″, ratio **2i**′:**2i**″ = 1.3:1) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (br, 1H, **2i″** isomer), 8.08 (br, 1H, **2i′** isomer), 7.95 (d, *J* = 7.9 Hz, 1H, **2i″** isomer), 7.85 (d, *J* = 8.2 Hz, 1H, **2i′** isomer), 7.69 (d, *J* = 7.2 Hz, 2H, **2i′** isomer), 7.59 (d, *J* = 8.0 Hz, 2H, **2i″** isomer), 7.50–7.40 (m, 2H, **2i′** isomer and 1H, **2i″** isomer), 7.36–7.17 (m, 3H, **2i′** isomer and 5H, **2i″** isomer, overlapped with $CDCl_3$), 7.05 (d, *J* = 8.2 Hz, 1H, **2i′** isomer), 2.51 (s, 3H, **2i′** isomer), 2.43 (s, 3H, **2i″** isomer) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (*C*, **2i′** isomer), 136.8 (*C*, **2i″** isomer), 135.9 (*C*), 135.7 (*C*), 132.7 (*C*, **2i′** isomer), 132.4 (*C*, **2i′** isomer), 129.6 (*C*H, **2i″** isomer), 128.9 (*C*H, **2i′** isomer), 127.6 (*C*H, **2i″** isomer), 127.5 (*C*H, **2i′** isomer), 126.0 (*C*H, both isomers), 123.7 (*C*, **2i′** isomer), 122.5 (*C*H, **2i″** isomer), 122.2 (*C*H, **2i′** isomer), 121.6 (*C*H, **2i″** isomer), 121.2 (*C*H, **2i′** isomer), 120.3 (*C*H, **2i″** isomer), 120.0 (*C*H, **2i″** isomer), 119.6 (*C*H, **2i′** isomer), 118.5 (*C*, **2i″** isomer), 118.3 (*C*, **2i′** isomer), 111.5 (*C*H, **2i″** isomer), 111.4 (*C*H, **2i′** isomer), 21.8 (CH_3, **2i″** isomer), 21.3 (CH_3, **2i″** isomer) ppm. Elemental Analysis for $C_{15}H_{13}N$ Calcd.: C, 86.92; H, 6.32; N, 6.76%. Found: C, 87.22; H, 6.57; N, 6.44%.

2-methyl-3-phenyl-1*H*-indole (2j). Obtained as a yellow gum (53 mg, 0.26 mmol, 47% yield) after column chromatography (hexane:AcOEt = 95:5 + 1% Et_3N). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.53 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.37–7.29 (m, 2H), 7.18 (td, *J* = 7.6, 1.1 Hz, 1H), 7.12 (td, *J* = 7.6, 1.1 Hz, 1H), 2.52 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (*C*), 135.4 (*C*), 131.5 (*C*), 129.6 (*C*H), 128.6 (*C*H), 128.0 (*C*), 125.9 (*C*H), 121.7 (*C*H), 120.1 (*C*H), 118.9 (*C*H), 114.7 (*C*), 110.4 (*C*H), 12.7 (CH_3) ppm. Elemental Analysis for $C_{15}H_{13}N$ Calcd.: C, 86.92; H, 6.32; N, 6.76%. Found: C, 87.18; H, 6.52; N, 6.55%.

4. Conclusions

In this work, we have extended the use of phenyl formate as a CO surrogate to the reductive cyclization of β-nitrostyrenes. Good results could be reached when a second aryl ring is present in the *alpha* position of the styrene. Depending on the substrate, results are comparable to or a little worse than those achievable by the use of pressurized gaseous CO. However, the reaction was not satisfactory when no aryl substituent was present in the *alpha* position of the nitrostyrene, at least when the results previously achieved by the use of pressurized CO are taken as a reference. That the latter substrates required harsher reaction conditions had already been noted, but this fact had only been imputed to a lower reactivity of starting nitroalkene. In this work, we have found that the lower reactivity is only one aspect of the problem. The other is that bases, necessary for the decomposition of phenyl formate, promote unwanted side reactions, apparently oligo- and polymerization reactions. Thus, a competition exists between the cyclization and the secondary reactions and the only efficient way of favoring the former is to increase the CO pressure. Even if the problem may be in theory solved by increasing the phenyl formate amount, this cannot be safely done in a glass pressure tube. For these substrates, the use of pressurized CO [36] seems to us to still be the best choice, but employing $Mo(CO)_6$ as a CO surrogate that does not require the presence of a base to be activated [39] appears anyway to allow for better results than those achievable by using phenyl formate.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/catal12010106/s1, Experimental details for the synthesis of the starting nitroalkenes. Figure S1: Picture of the pressure tube and heating apparatus employed. Figures S2–S22: copies of NMR spectra.

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