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Use of Phenyl Formate as a CO Surrogate for the Reductive Cyclization of Organic Nitro Compounds to Yield Different *N*-Heterocycles: Avoiding the Use of Autoclaves and Pressurized Gases †

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Abstract: The reductive cyclization of different organic nitro compounds by carbon monoxide, catalyzed by transition metal complexes, is a very efficient and clean strategy for the synthesis of many *N*-heterocycles. However, it requires the use of autoclaves and pressurized CO lines. In this paper, the authors will present the results obtained in their laboratories on the use of phenyl formate as a convenient CO surrogate, able to liberate carbon monoxide under reaction conditions and allowing for the use of a cheap glass pressure tube as a reaction vessel. In most cases, yields were better than those previously reported using pressurized CO, proving that the use of CO surrogates can be a viable alternative to the gaseous reagent.

Keywords: nitroarenes; nitroalkenes; indoles; carbazoles; oxazines; palladium; carbon monoxide; CO surrogate; homogeneous catalysis; carbonylation reactions

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1. Introduction

Nitrogen heterocycles are useful structures in the pharmaceutical chemistry, and enormous efforts are continuously made to improve their synthesis. Among the numerous possible synthetic approaches, the reductive cyclization of nitroarenes and nitroalkenes by carbon monoxide, catalyzed by transition metal complexes, is synthetically appealing because of the easy availability of the reagents and the facile separation of the only stoichiometric byproduct: CO_2 [1–3]. However, it requires the use of high-pressure equipment and pressurized CO lines, which often are not available. The problem is also common to other carbonylation reactions, and, in the last decade, different solid or liquid substances able to liberate CO under reaction conditions have been developed [4–7]. Several years ago, we started to investigate the use of formate esters as CO surrogates in the field of reductive cyclization reactions of organic nitro compounds, because they are cheap and non- or barely toxic, and because the stoichiometric byproduct, an alcohol or phenol, is unlikely to interfere with the reaction course. In this paper, our results are summarized.

2. Results

2.1. General Aspects

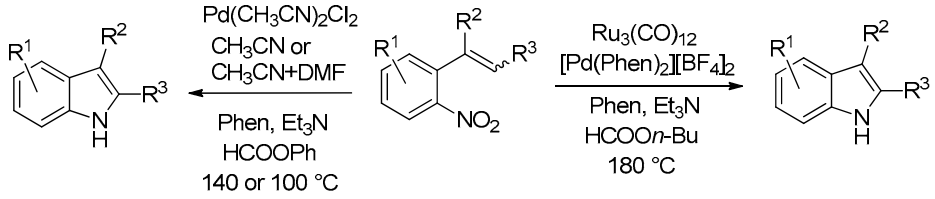
Before discussing the synthesis of individual heterocycles, we will summarize some general trends in the reactivity of nitro compounds with CO.

1. Palladium, ruthenium and rhodium compounds have all been employed as catalysts, but the best results have been obtained through the use of palladium.

2. The best ligands, in terms of activity and stability of the catalytic system, are phenanthroline and its substituted derivatives. Phosphines have been used as ligands in many cases, but they are oxidized to phosphinoxides during the reaction.
3. Aryl formates can be decomposed into CO and phenols, even by weak organic bases. Alkyl formates are cheaper, but they are activated only by very strong bases, which would not be compatible with most reactions. Alternatively, they can be decomposed via the action of a ruthenium-based catalytic system.
4. When using CO surrogates, the reaction must be performed in a so-called "pressure tube", which is a thick-walled vessel sealable using a PTFE or PTFE-lined screw cap.

2.2. Synthesis of Indoles from o-Nitrostyrenes

The first reaction we tried to accomplish, using formate esters as CO surrogates, was the synthesis of indoles from *o*-nitrostyrenes (Scheme 1) [8–10].



Scheme 1. Synthesis of indoles from *o*-nitrostyrenes.

Initially, we attempted to use alkyl formates as CO surrogates (Scheme 1, right side) [11]. A palladium catalyst alone was inactive, as no formate decomposition occurs in its presence when a weak base is present. A second catalyst, $Ru_3(CO)_{12}$, was necessary. Yet, a high 180 °C temperature was required for efficient formate decomposition, and the synthetic results were not satisfactory, with a maximum indole yield of around 70%.

The use of aryl formates, the best phenyl formate, allowed us to achieve much better results and to employ palladium alone as a catalyst, thus simplifying the catalytic system (Scheme 1, left side). This catalytic system was subjected to two optimization studies. During the first, the temperature was set at 140 °C. Almost quantitative yields were achieved in several cases, but substrates bearing sensitive groups still gave unsatisfactory results [11]. Thus, we engaged in a second round of optimization of the reaction conditions, and we succeeded in finding a set of experimental conditions that worked at 100 °C with as little as 0.2 mol% palladium [12].

The main synthetic results are reported in Figure 1, where the yields obtained under different conditions are also compared. It should be noted that whenever a comparison is possible, the obtained yields are, in most cases, higher than the best previously reported yields for the same reaction employing pressurized CO as a reductant. Only in a few cases did the reaction fail to yield an isolable indole.

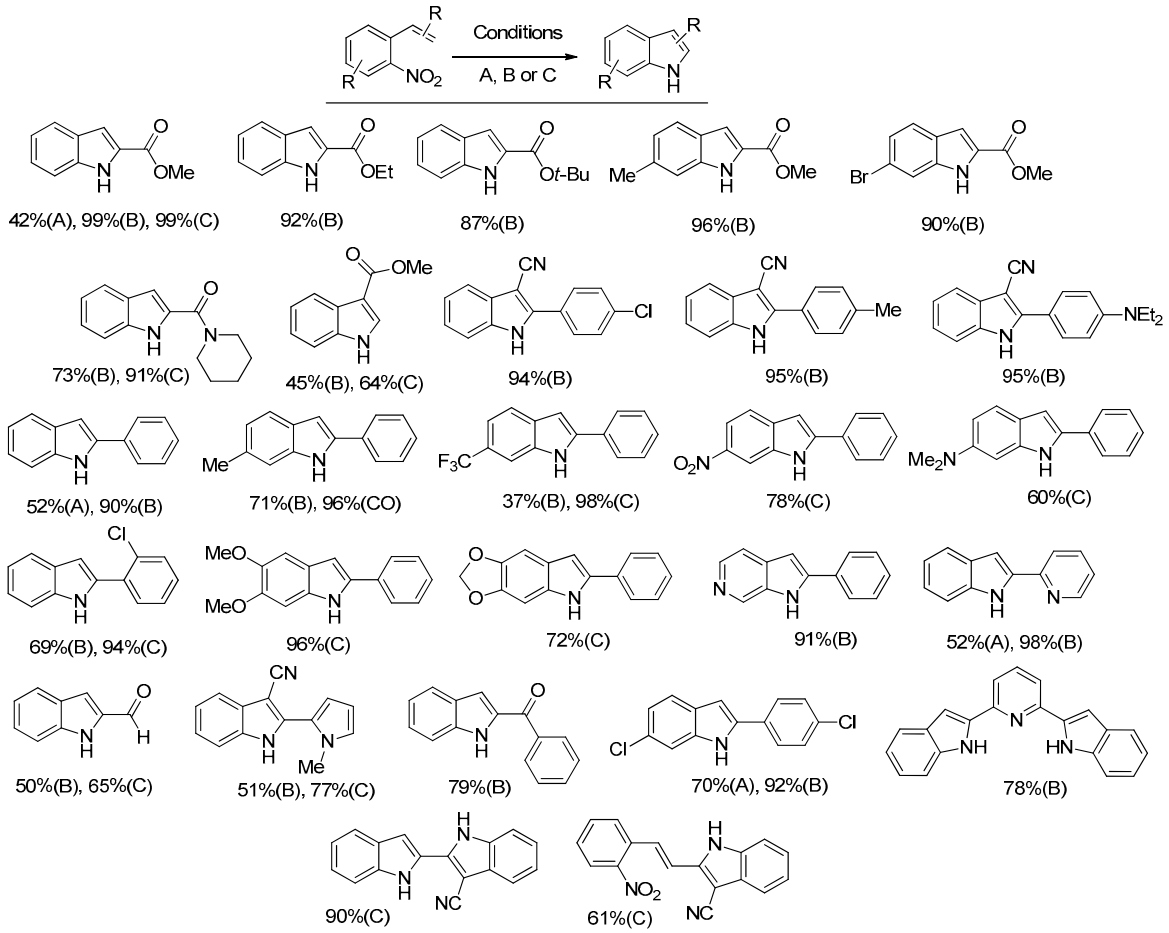
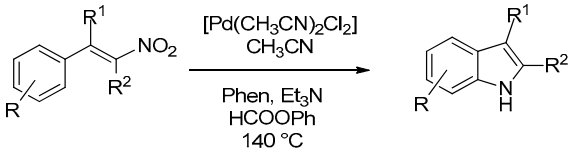


Figure 1. Indoles from *o*-nitrostyrenes. Conditions A: 0.27 mmol nitrostyrene, 1 mol% $[Pd(Phen)_2][BF_4]_2$, 1 mol% $Ru_3(CO)_{12}$, 20 mol% Phen, and 40 µL Et_3N, in butyl formate (10 mL), at 180 °C for 10 h. Conditions B: 0.54 mmol nitrostyrene, 1 mol% $Pd(CH_3CN)_2Cl_2$, 2.5 mol% Phen, 240 µL HCOOPh, 40 µL Et_3N, in CH_3CN (10 mL), at 140 °C for 3 h. Conditions C: 0.54 mmol nitrostyrene, 1 mol% $Pd(CH_3CN)_2Cl_2$, 5 mol% Phen, 260 µL HCOOPh, 100 µL Et_3N, in CH_3CN + DMF (9+1 mL), at 100 °C for 6 h.

2.3. Synthesis of Indoles from β-Nitrostyrenes

The reactions described in the previous paragraph are very selective, but the synthesis of the starting *o*-nitrostyrene is not always high yielding. In some cases, synthesizing a β-nitrostyrene, where the nitro group is on the olefin moiety, is more straightforward.

The reductive cyclization of β-nitrostyrenes was reported by Dong [13] and by us [14]. We thus decided to test the use of phenyl formate as a CO surrogate for this reaction (Scheme 2).



Scheme 2. Synthesis of indoles from β-nitrostyrenes.

Despite some effort in optimizing the experimental conditions, only fair yields could be obtained in the case of β-nitrostyrenes lacking any substituent in the *alpha* position. It was found that bases catalyze the oligo/polymerization of the nitrostyrene itself. Better results

were obtained with α-aryl-β-nitrostyrenes, which are more reactive towards reductive cyclization and less prone to polymerization. The substrate scope is shown in Figure 2 [15].

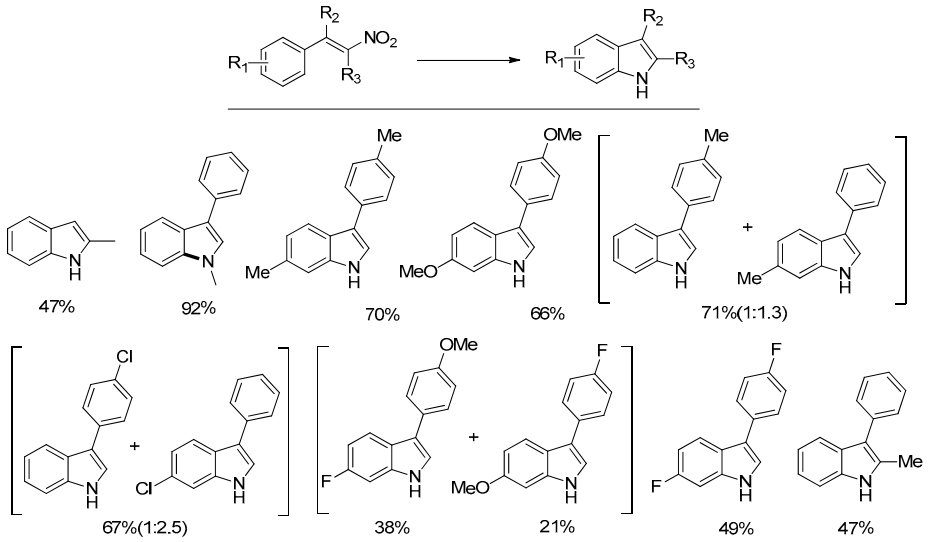


Figure 2. Synthesis of indoles from β-nitrostyrenes. Experimental conditions: 0.54 mmol nitrostyrene, 1 mol% $PdCl_2(CH_3CN)_2$, 5 mol% Phen, 260 μL PhOC(O)H, 120 μL Et_3N, in 10 mL CH_3CN, at 140 °C for 4 h.

2.4. Synthesis of 3,6-dihydro-2H-[1,2]-Oxazines from Nitroarenes and Conjugated Dienes

Free nitrosoarenes quickly react with conjugated dienes in a hetero-Diels–Alder reaction to give 3,6-dihydro-2*H*-[1,2]-oxazines [16]. However, the synthesis of nitrosoarenes is not straightforward. The trapping of nitrosoarenes intermediately formed during the reduction of nitroarenes is an effective strategy to synthesize oxazines [17,18]. The experimental conditions, initially optimized for the synthesis of indoles using phenyl formate as a CO surrogate, proved to also be suitable for the synthesis of oxazines [19].

The synthetic results are shown in Figure 3. Excellent results were obtained in many cases. The reaction only failed when the nitroarene bore strongly electron-donating substituents and when both the terminal positions of the diene were substituted. In the first case, the reason is the low dienophile character of the electron-rich nitrosoarenes, and in the second, the reversibility of the formation of oxazine at a high temperature.

2.5. Synthesis of Carbazoles from o-Nitrobiphenyls

The cyclization of *o*-nitrobiphenyls to carbazoles under the reducing action of carbon monoxide has long been known [20], but has been little developed with respect to the synthesis of indoles because it requires harsher conditions and affords lower yields of the desired heterocycle. Wishing to solve the problem, we decided to apply our phenyl formate protocol to this interesting reaction. Initial attempts were disappointing, but optimization of the reaction conditions allowed us to reach high yields of the desired products. The key points for success proved to be the use of DMF as a solvent, and of an inorganic base, the best being Na_3PO_4, in place of Et_3N. The synthetic results are shown in Figure 4. The yields are generally higher than those previously obtained through the use of pressurized CO [21].

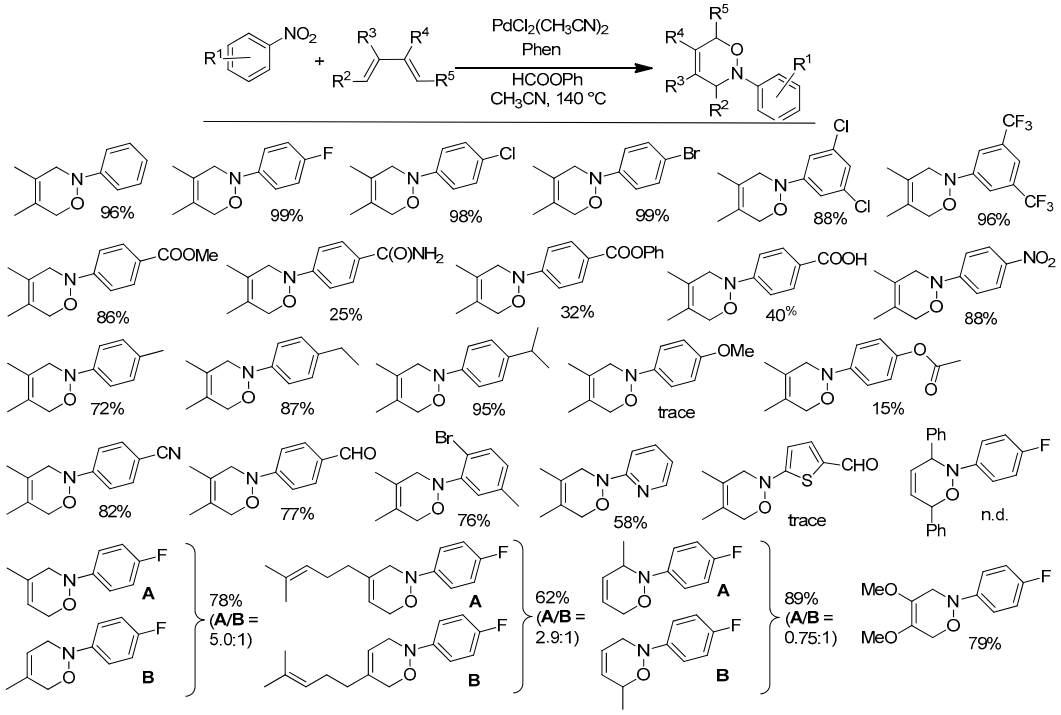


Figure 3. Synthesis of oxazines from nitroarenes and conjugated dienes. Experimental conditions: nitroarene 0.54 mmol, $Pd(CH_3CN)_2Cl_2$ 1 mol%, Phen 2.5 mol%, diene 4 equiv, HCOOPh 2.2 mmol, Et_3N 0.27 mmol, in 10 mL CH_3CN, at 140 °C for 4 h.

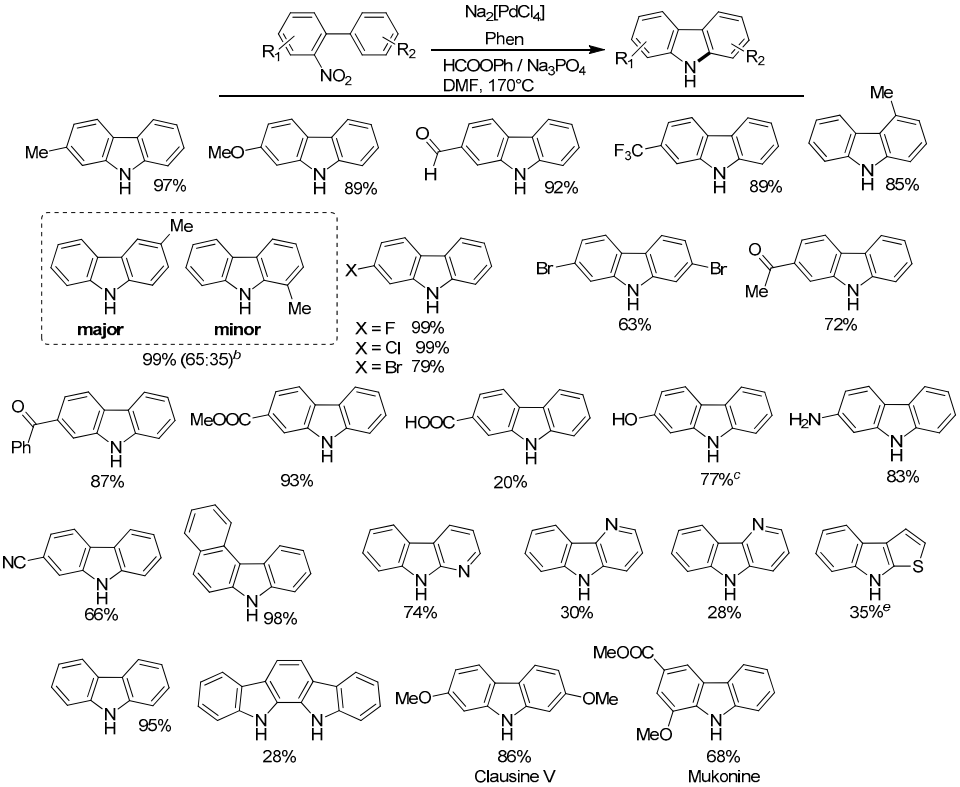


Figure 4. Synthesis of carbazoles from *o*-nitrobiphenyls. Experimental conditions: nitrobiphenyl (0.54 mmol), $Na_2[PdCl_4]$ (1 mol%), Phen (5 mol%) HCOOPh (2.4 mmol), Na_3PO_4 (7.3×10^{-2} mmol) in DMF (10 mL) for 5 h.

3. Conclusions

The use of CO as a reductant for nitroarenes and nitroalkenes presents many advantages from a synthetic point of view, but is operationally complex for many groups. In this brief presentation, we presented our results on the use of formate esters as convenient CO surrogates. In particular, phenyl formate can be activated even by weak bases, which do not interfere or even have a beneficial role in the reactions. It is worth noting that in most cases, the isolated yields in the desired heterocycle were higher than those previously obtained for the same reaction when gaseous CO, or even another reductant, had been employed. The only exception is the cyclization of β-nitrostyrenes to indoles. The reason is that in order to give good results, this reaction requires CO pressures that are too high to be withstood by a glass pressure tube. The high yields obtained in the other cases clearly show that the use of a CO surrogate should not necessarily be considered as a second choice when the use of pressurized CO is not possible, but may represent the best available option in some cases.

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References

1. Ferretti, F.; Ramadan, D.R.; Ragaini, F. Transition Metal Catalyzed Reductive Cyclization Reactions of Nitroarenes and Nitroalkenes. *ChemCatChem* **2019**, *11*, 4450–4488. [CrossRef]
2. Ragaini, F.; Cenini, S.; Gallo, E.; Caselli, A.; Fantauzzi, S. Fine chemicals by reductive carbonylation of nitroarenes, catalyzed by transition metal complexes. *Curr. Org. Chem.* **2006**, *10*, 1479–1510. [CrossRef]
3. Soderberg, B.C.G. Synthesis of heterocycles via intramolecular annulation of nitrene intermediates. *Curr. Org. Chem.* **2000**, *4*, 727–764. [CrossRef]
4. Konishi, H.; Manabe, K. Formic Acid Derivatives as Practical Carbon Monoxide Surrogates for Metal-Catalyzed Carbonylation Reactions. *Synlett* **2014**, *25*, 1971–1986. [CrossRef]
5. Friis, S.D.; Lindhardt, A.T.; Skrydstrup, T. The Development and Application of Two-Chamber Reactors and Carbon Monoxide Precursors for Safe Carbonylation Reactions. *Acc. Chem. Res.* **2016**, *49*, 594–605. [CrossRef]
6. Gautam, P.; Bhanage, B.M. Recent advances in the transition metal catalyzed carbonylation of alkynes, arenes and aryl halides using CO surrogates. *Catal. Sci. Technol.* **2015**, *5*, 4663–4702. [CrossRef]
7. Chen, Z.; Wang, L.-C.; Wu, X.-F. Carbonylative synthesis of heterocycles involving diverse CO surrogates. *Chem. Commun.* **2020**, *56*, 6016–6030. [CrossRef]
8. Tollari, S.; Cenini, S.; Crotti, C.; Gianella, E. Synthesis of heterocycles via palladium-catalyzed carbonylation of ortho-substituted organic nitro compounds in relatively mild conditions. *J. Mol. Catal.* **1994**, *87*, 203–214. [CrossRef]
9. Ansari, N.H.; Banini, S.; Cummings, M.M.; Söderberg, B.C.G. Palladium-Catalyzed Double Reductive Cyclization of 2,3-Dinitro-1,4-dialkenylbenzenes. Synthesis of 1*H*,8*H*-Pyrrolo[3,2-g]indoles. *J. Org. Chem.* **2020**, *85*, 4002–4010. [CrossRef]
10. Soderberg, B.C.; Shriver, J.A. Palladium-catalyzed synthesis of indoles by reductive N-heteroannulation of 2-nitrostyrenes. *J. Org. Chem.* **1997**, *62*, 5838–5845.
11. Formenti, D.; Ferretti, F.; Ragaini, F. Synthesis of N-Heterocycles by Reductive Cyclization of Nitro Compounds using Formate Esters as Carbon Monoxide Surrogates. *ChemCatChem* **2018**, *10*, 148–152. [CrossRef]
12. Fouad, M.A.; Ferretti, F.; Formenti, D.; Milani, F.; Ragaini, F. Synthesis of Indoles by Reductive Cyclization of Nitro Compounds Using Formate Esters as CO Surrogates. *Eur. J. Org. Chem.* **2021**, *2021*, 4876–4894. [CrossRef]
13. Hsieh, T.H.H.; Dong, V.M. Indole synthesis: Palladium-catalyzed C-H bond amination via reduction of nitroalkenes with carbon monoxide. *Tetrahedron* **2009**, *65*, 3062–3068. [CrossRef]
14. Ferretti, F.; El-Atawy, M.A.; Muto, S.; Hagar, M.; Gallo, E.; Ragaini, F. Synthesis of Indoles by Palladium-Catalyzed Reductive Cyclization of β-Nitrostyrenes with Carbon Monoxide as the Reductant. *Eur. J. Org. Chem.* **2015**, *2015*, 5712–5715. [CrossRef]

15. Ferretti, F.; Fouad, M.A.; Ragaini, F. Synthesis of Indoles by Palladium-Catalyzed Reductive Cyclization of β-Nitrostyrenes with Phenyl Formate as a CO Surrogate. *Catalysts* **2022**, *12*, 106. [CrossRef]
16. Yamamoto, H.; Kawasaki, M. Nitroso and azo compounds in modern organic synthesis: Late blooming but very rich. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595–607. [CrossRef]
17. Ragaini, F.; Rapetti, A.; Visentin, E.; Monzani, M.; Caselli, A.; Cenini, S. Synthesis of indoles by intermolecular cyclization of unfunctionalized nitroarenes and alkynes, catalyzed by palladium-phenanthroline complexes. *J. Org. Chem.* **2006**, *71*, 3748–3753. [CrossRef]
18. Ragaini, F.; Ventriglia, F.; Hagar, M.; Fantauzzi, S.; Cenini, S. Synthesis of Indoles by Intermolecular Cyclization of Unfunctionalized Nitroarenes and Alkynes: One-Step Synthesis of the Skeleton of Fluvastatin. *Eur. J. Org. Chem.* **2009**, *2009*, 2185–2189. [CrossRef]
19. EL-Atawy, M.A.; Formenti, D.; Ferretti, F.; Ragaini, F. Synthesis of 3,6-Dihydro-2*H*-[1,2]-Oxazines from Nitroarenes and Conjugated Dienes, Catalyzed by Palladium/Phenanthroline Complexes and Employing Phenyl Formate as a CO Surrogate. *ChemCatChem* **2018**, *10*, 4707–4717. [CrossRef]
20. Crotti, C.; Cenini, S.; Bassoli, A.; Rindone, B.; Demartin, F. Synthesis of carbazole by triruthenium dodecacarbonyl catalyzed reductive carbonylation of 2-nitrobiphenyl: The crystal and molecular structure of $Ru_3(\mu_3\text{-}NC_6H_4\text{-}o\text{-}C_6H_5)_2(CO)_9$. *J. Mol. Catal.* **1991**, *70*, 175–187. [CrossRef]
21. Ramadan, D.R.; Ferretti, F.; Ragaini, F. Catalytic reductive cyclization of 2-nitrobiphenyls using phenyl formate as CO surrogate: A robust synthesis of 9*H*-carbazoles. *J. Catal.* **2022**, *409*, 41–47. [CrossRef]