

Proceeding Paper

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 [†]

Fabio Ragaini ^{1,*}, Francesco Ferretti ¹ and Manar Ahmed Fouad ^{1,2}

¹ Dipartimento di Chimica, Università degli Studi di Milano, via C. Golgi 19, 20133, Milano (Italy)

² Chemistry Department, Faculty of Science, Alexandria University, P.O. Box 426, Alexandria 21321, Egypt

* Correspondence: fabio.ragaini@unimi.it

[†] Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry; Available online: <https://ecsoc-26.sciforum.net>.

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, its use requires the use of autoclaves and pressurized CO lines. In this talk, the author will present the results obtained in his laboratories on the use of phenyl formate as a convenient CO surrogate, able to liberate carbon monoxide under the reaction conditions and allowing the use of a cheap glass pressure tube as a reaction vessel. In most cases, yields were better than those previously reported by the use of 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

Citation: Ragaini, F.; Ferretti, F.; Fouad, M.A. 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. *2022*, *4*, x.

<https://doi.org/10.3390/xxxxx>

Academic Editor(s):

Published: 15 November 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Nitrogen heterocycles are privileged structures in pharmaceutical chemistry and an enormous effort is continuously done 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: CO₂ [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 the 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, non- or little-toxic and because the stoichiometric byproduct, an alcohol or phenol, is unlikely to interfere with the reaction course. In this account, our results in the field are summarized.

2. Results

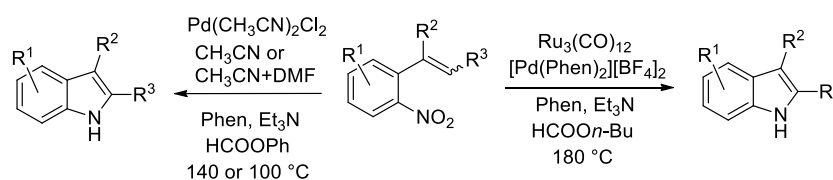
2.1. General Aspects

Before discussing the synthesis of the 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 best results have been obtained by 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 phosphinioxides 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 by 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 by 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, alkyl formates were attempted 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, $\text{Ru}_3(\text{CO})_{12}$ 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 around 70 %.

The use of aryl formates, best phenyl formate, allowed us to achieve much better results and to employ just palladium as 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 could be 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, which allow to work 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 the reaction failed to yield an isolable indole.

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.

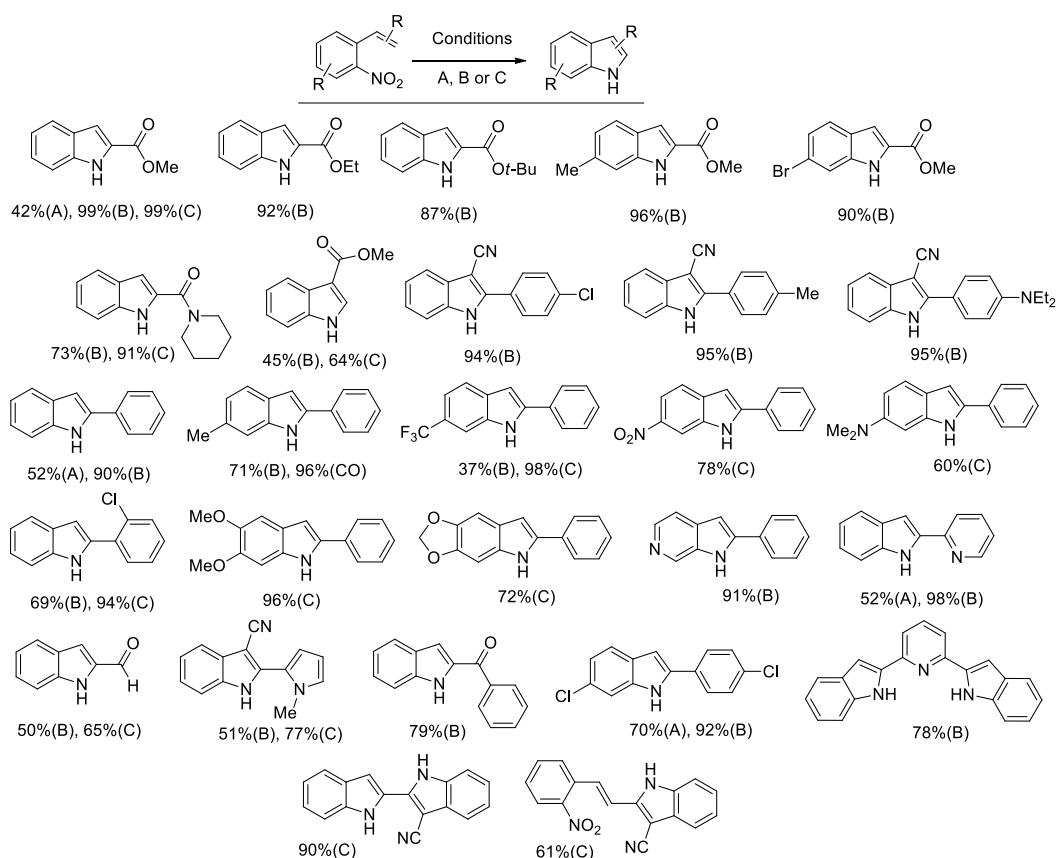
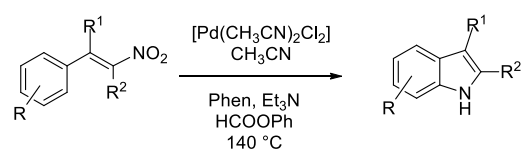


Figure 1. Indoles from *o*-nitrostyrenes. Conditions A: 0.27 mmol nitrostyrene, mol. 1 mol % $[\text{Pd}(\text{Phen})_2][\text{BF}_4]_2$, 1 mol % $\text{Ru}_3(\text{CO})_{12}$, 20 mol % Phen; mol. 40 μL Et_3N ; in butyl formate (10 mL), at 180 °C for 10h. Conditions B: 0.54 mmol nitrostyrene, 1 mol % $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$, 2.5 mol % Phen, 240 μL HCOOPh , 40 μL Et_3N , in CH_3CN (10 mL), 140 °C for 3 h. Conditions C: 0.54 mmol nitrostyrene, 1 mol % $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$, 5 mol % Phen, 260 μL HCOOPh , 100 μL Et_3N , in CH_3CN + DMF (9+1 mL), at 100 °C for 6 h.

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 α 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 the reductive cyclization and less prone to polymerization. The substrate scope is shown in Figure 2 [15].

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-2H-[1,2]-oxazines [16]. However, the synthesis of nitrosoarenes is not straightforward. 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 be also suitable for the synthesis of oxazines [19].

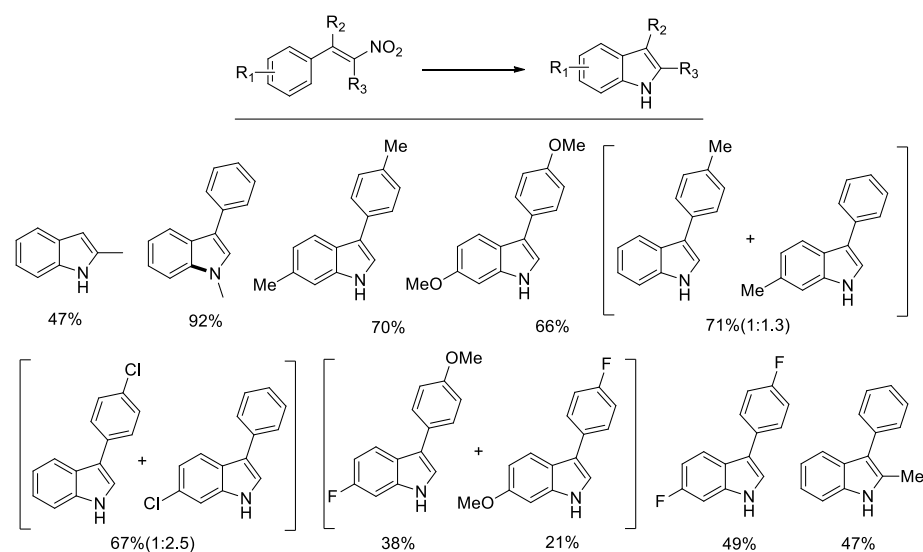


Figure 2. Synthesis of indoles from β -nitrostyrenes. Experimental conditions: 0.54 mmol nitrostyrene, 1 mol% $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, 5 mol% Phen, 260 μL PhOC(O)H , 120 μL Et_3N , in 10 mL CH_3CN , at 140 $^\circ\text{C}$ for 4 h.

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

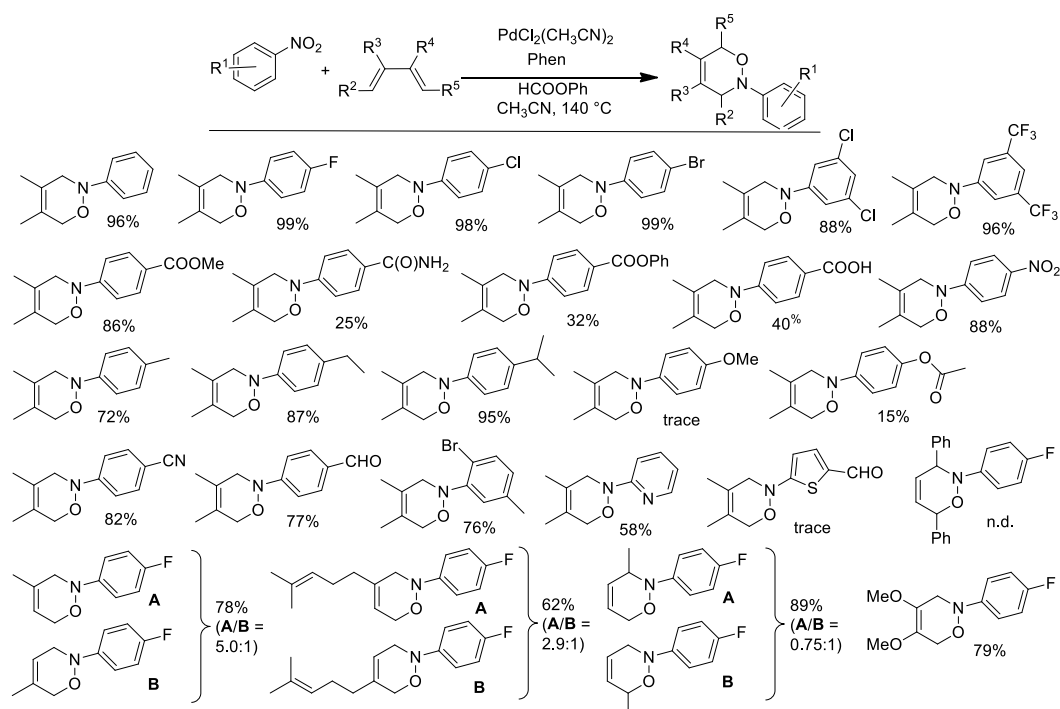


Figure 3. Synthesis of oxazines from nitroarenes and conjugated dienes. Experimental conditions: nitroarene 0.54 mmol, $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ 1 mol %, Phen 2.5 mol %, diene 4 equiv, HCOOPh 2.2 mmol, Et_3N 0.27 mmol, in 10 mL CH_3CN , at 140 $^\circ\text{C}$ for 4 h.

2.4. Synthesis of Carbazoles from *o*-nitrobiphenyls

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 to reach high yields of the desired products. Key points for success proved to be the use of DMF as solvent and of an inorganic base, best Na₃PO₄ in place of Et₃N. Synthetic results are shown in Figure 4. Yields are in general higher than those previously obtained by the use of pressurized CO [21].

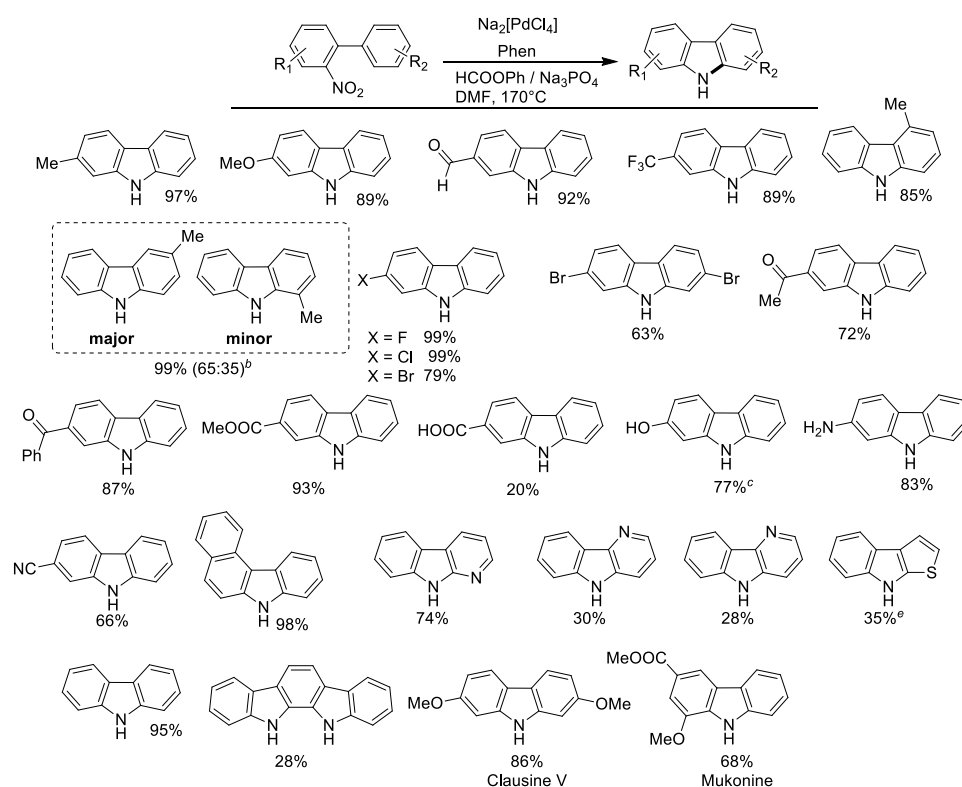


Figure 4. Synthesis of carbazoles from *o*-nitrobiphenyls. Experimental conditions: nitrobiphenyl (0.54 mmol), $\text{Na}_2[\text{PdCl}_4]$ (1 mol %), Phen (5 mol %), HCOOPh (2.4 mmol), Na_3PO_4 (7.3×10^{-2} mmol) in DMF (10 mL), for 5 h.

3. Conclusions

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 have 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. Worth of note, in most cases the isolated yield in the desired heterocycle were higher than those previously obtained for the same reaction when gaseous CO or even other 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 too high CO pressures to be withstood by a glass pressure tube. The high yields obtained in the other cases clearly show that the use of a CO surrogates 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 any case.

Author Contributions: Conceptualization, F.R.; writing—original draft preparation, F.R.; writing—review and editing, F.F. and M.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Università degli Studi di Milano, PSR 2020-project: “Sustainable catalytic strategies for the synthesis of high added-value fine-chemicals”.

Data Availability Statement: Data supporting the information given in this account can be found on the original publications, which are cited in the references.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ferretti, F.; Ramadan, D.R.; Ragaini, F. “Transition Metal Catalyzed Reductive Cyclization Reactions of Nitroarenes and Nitroalkenes” *ChemCatChem* **2019**, *11*, 4450–4488.
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.
3. Soderberg, B.C.G. “Synthesis of heterocycles via intramolecular annulation of nitrene intermediates” *Curr. Org. Chem.* **2000**, *4*, 727–764.
4. Konishi, H.; Manabe, K. “Formic Acid Derivatives as Practical Carbon Monoxide Surrogates for Metal-Catalyzed Carbonylation Reactions” *Synlett* **2014**, *25*, 1971–1986.
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.
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.
7. Chen, Z.; Wang, L.-C.; Wu, X.-F. “Carbonylative synthesis of heterocycles involving diverse CO surrogates” *Chem. Commun.* **2020**, *56*, 6016–6030.
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.
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.
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.
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**, 4876–4894.
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.
14. Ferretti, F.; El-Atawy, M.A.; Muto, S.; Hagar, M.; Gallo, E.; Ragaini, F. “Synthesis of Indoles by Palladium-Catalyzed Reductive Cyclization of *b*-Nitrostyrenes with Carbon Monoxide as the Reductant” *Eur. J. Org. Chem.* **2015**, 5712–5715.
15. Ferretti, F.; Fouad, M.A.; Ragaini, F. “Synthesis of Indoles by Palladium-Catalyzed Reductive Cyclization of *b*-Nitrostyrenes with Phenyl Formate as a CO Surrogate” *Catalysts* **2022**, *12*, 106.
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.
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.
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**, 2185–2189.
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.
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 $\text{Ru}_3(\text{m}_3\text{-NC}_6\text{H}_4\text{-o-C}_6\text{H}_5)_2(\text{CO})_9$ ” *J. Mol. Catal.* **1991**, *70*, 175–187.
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.