

The Reduction of Organic Nitro Compounds by Carbon Monoxide as an Effective Strategy for the Synthesis of *N*-Heterocyclic Compounds: a Personal Account

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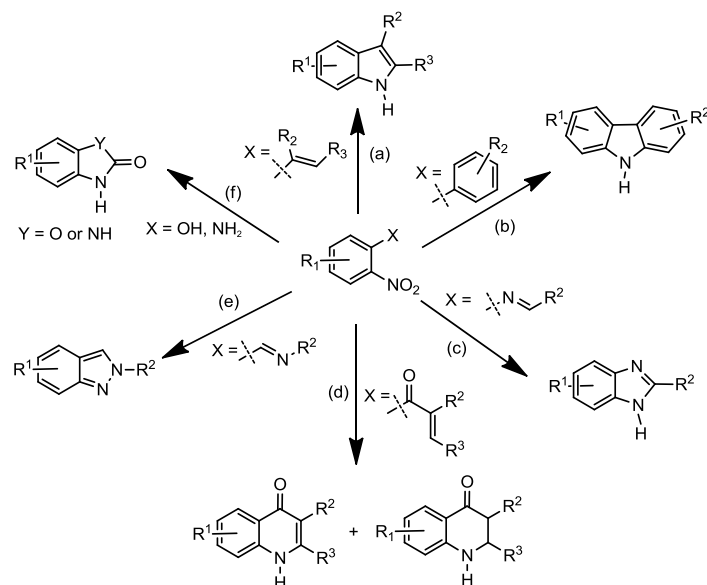
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Abstract:

Reduction of suitably substituted organic nitro compounds by CO, catalyzed by different metal complexes, affords a variety of *N*-heterocyclic compounds. Carbon dioxide is the only stoichiometric byproduct. Several *inter*-molecular condensations have also been developed during the year in which a nitroarene and an alkene, diene or alkyne are reacted together to afford indoles, pyrroles, oxazines or allylic amines. This account focusses on the results obtained by our group in this field in the last 30 years. A special attention is given to the more recently developed *inter*-molecular reactions.

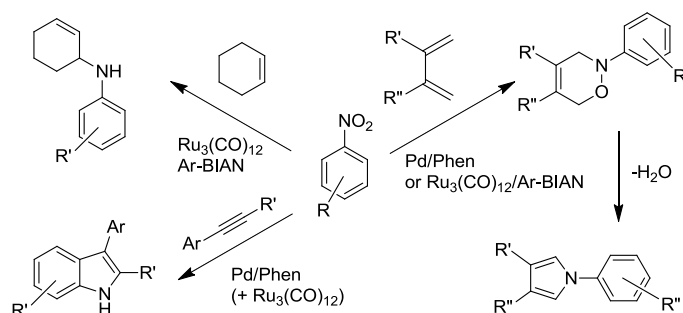
Introduction

Nitrogen heterocycles are ubiquitous in all fields of chemistry, from pharmaceutical compounds to polymers, and their synthesis continue to attract an enormous attention. One of the many possible synthetic strategies relies on the ability of nitroarenes to originate a new heterocyclic ring by reaction with a pendant unsaturated group or an external unsaturated molecule, when deoxygenated by a suitable reducing agent. Phosphines and phosphites were originally employed to this aim and the corresponding chemistry was developed mainly by Cadogan and Sundberg (Soderberg 2000). However, experimental conditions are usually harsh, the phosphine oxides or the phosphites which are formed as stoichiometric byproducts can be difficult to separate from the organic products of the reactions and, last but not least, the reaction are very far from being atom-economical, a requisite of increasing importance for industrial applications. During the last 50 years, it has emerged that carbon monoxide can be employed as an effective and clean reductant for nitroarenes when suitable transition metal complexes are used as catalysts, CO₂ being the only stoichiometric byproduct. This chemistry originally developed from the need to find a strategy for the synthesis of isocyanates, alternative to the current technology employing highly toxic phosgene (Ragaini 2009), but it soon became apparent that when the nitroarene bears a suitable, usually unsaturated, group in the *ortho* position, cyclization strongly prevails over carbonylation. Some of the possible substrate/product combinations are shown in Scheme 1.



Scheme 1. Selected *intra*-molecular nitroarene cyclization reactions

More recently, some cases have been reported of cyclization reactions in which the unsaturated group is initially on a separate molecule with respect to the nitroarene (Scheme 2).



Scheme 2. *Inter*-molecular nitroarene cyclization reactions

We have previously reviewed this chemistry in a chapter book and in an independent paper (Cenini and Ragaini 1996; Ragaini et al. 2006a). In this account, we will focus on our own contribution to the field, although some works by others will also be mentioned when relevant. The synthesis of allylic amines will also be included, though they are not heterocycles, because it is mechanistically related to other reactions here described, but the synthesis of other nitrogen compounds such as isocyanates, carbamates, ureas and azo- and azoxyarenes will only be mentioned if mechanistically relevant to the formation of a *N*-heterocyclic compound. Some general reactivity trends and mechanistic information will also be given. *Intra*-molecular cyclization reactions will only be discussed in the context of general trends, whereas *inter*-molecular reactions will be discussed in more detail because, in our view, are synthetically more interesting. A separate paragraph is devoted to nitroalkenes.

General trends and *intra*-molecular cyclization reactions.

Activation of the nitro group

Electrochemical reduction of nitroarenes is well known to start with a single electron transfer to the nitroarene. The reaction of nitroarenes with transition metal complexes has been shown to involve a single electron transfer from the metal to the nitroarene in all cases in which it has been investigated, namely with complexes of nickel (Berman and Kochi 1980), ruthenium (Kunin et al. 1989; Skoog and Gladfelter 1997), iron (Belousov 2007; Belousov and Kolosova 1987; Ragaini 1996; Ragaini et al. 1995), and rhodium (Liu et al. 1995; Ragaini et al.

1992; Ragaini et al. 1994). Although direct involvement of radicals in the reaction of nitroarenes with palladium complexes has not been reported, evidence for radical formation in the activation of nitrosoarenes has been gained (Gallo et al. 1999; Tomson et al. 2011). Accordingly, only complexes in which the metal is in a low oxidation state, zero or even negative (Pd(0), Ni(0), Fe(0), Ru(0), Rh(-I) and neutral or negatively charged carbonyl clusters of these metals), are able to catalytically activate nitroarenes. Low valent metal complexes of other metals can also effect the reduction, but the reduced metal cannot be regenerated by the effect of CO and no catalytic cycle is possible. It should be noted that the literature abounds with mechanistic proposals in which higher oxidation state complexes are shown to activate nitroarenes, usually by nucleophilic attack on a coordinated CO. However, nitroarenes are among the weakest nucleophiles known and it should be stressed that no experimental evidence at all has ever been reported for such an activation mode. Metal carbonyl hydrides can act as activators, but only if they are electro-rich enough to act as electron donors, otherwise they are inactive (Ragaini 2009). The ability to transfer a hydrogen atom to the nitroarene is not the key point for activation. The radical couple formed during the initial activation step apparently remains in a solvent cage and rapidly collapses, because radical coupling products of the nitroarene have never been observed.

In accord with this view, nitroalkanes, which are much more difficult to reduce than nitroarenes, cannot be employed as substrates in any of the reaction discussed in this review. Although in one case we could isolate a palladium complex derived from nitromethane with the same structure of that derived from nitrobenzene (Masciocchi et al. 1998), that complex was catalytically inactive.

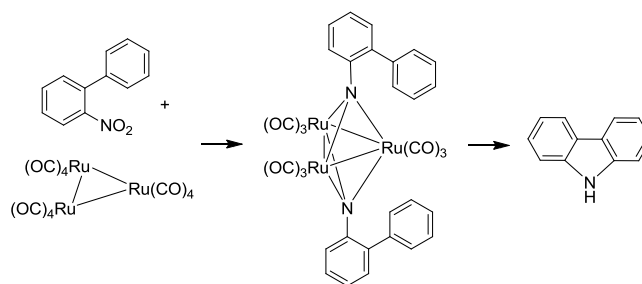
Nitroalkenes constitute a class of reagents that only very recently has been employed as substrates. Their reduction potential is intermediate between those of nitroarenes and nitroalkanes and their activation by metal complexes is possible, although it may require somewhat higher temperatures.

Reaction intermediates

It is generally agreed that the reduction of nitroarenes by CO proceeds through the intermediate formation of nitrosoarenes. Despite the fact that isolation of nitrosoarene complexes after a reaction of a nitroarene with a metal carbonyl complex is a rare event (Koerner von Gustorf and Jun 1965; Skoog et al. 1994), several cases have been reported in which the initially formed nitrosoarene complex insert the coproduced CO₂ and/or another CO molecule to yield different types of metallacyclic compounds in which the Ar-NO moiety is still identifiable (Gargulak et al. 1991; Leconte et al. 1990; Masciocchi et al. 1998; Paul et al. 1993; Paul et al. 1998; Ragaini et al. 1992; Ragaini et al. 1994; Sessanta o Santi et al. 1997). Moreover, the identification of several organic products clearly deriving from a reaction of a nitrosoarene (*vide infra*) also strongly supports this view.

Nitrosoarenes are a class of compounds with a rich chemistry in its own, both when in conjunction with metal complexed or not (Adam and Krebs 2003; Beaudoin and Wuest 2016; Bodnar and Miller 2011; Gowenlock and Richter-Addo 2008; Kogan 1986; Tomson et al. 2011; Yamamoto and Momiyama 2005). Some of these reactions will be considered in the following discussion.

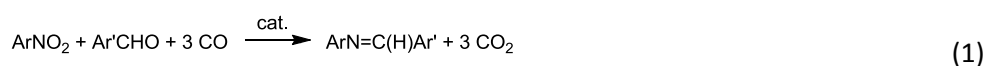
Especially in the older literature, the intermediate responsible for the cyclization step was proposed to be an imido complex (sometimes improperly called a nitrene complex). We also made this proposal in the earliest reported example of cyclization of *N*-(2-nitrophenyl)phenylmethanimine derivatives to give the corresponding 2-substituted benzimidazoles (Path c in Scheme 1, catalyst = Ru₃(CO)₁₂) (Crotti et al. 1992). The proposal was based on the previous isolation by other members of the same group of a *bis*-imido trinuclear cluster, Ru₃(μ₃-C₆H₄-*o*-C₆H₅)₂(CO)₉, from the reaction of Ru₃(CO)₁₂ with *o*-nitrobiphenyl (Crotti et al. 1991). This cluster afforded the expected cyclization product, carbazole, upon heating, albeit only in low yields (Scheme 3; see also Path b in Scheme 1).



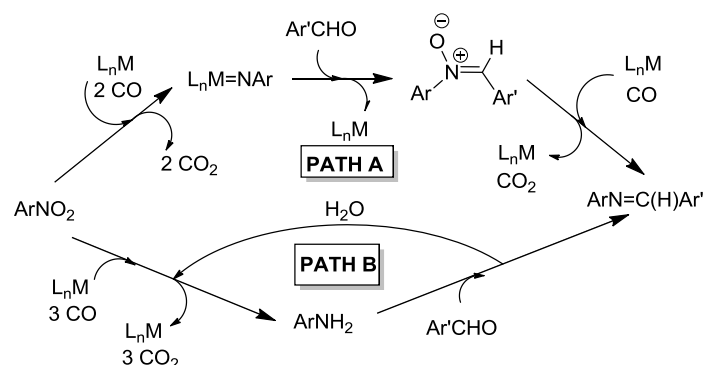
Scheme 3. Initial proposal for the formation of carbazole

It should be noted that at the time it was generally agreed that μ_3 -imido trinuclear ruthenium and iron clusters played a role in the carbonylation of nitrobenzene to give isocyanates or carbamates or in the reduction by CO/H₂O of nitroarenes to give aniline with both ruthenium (Cenini et al. 1988a; Cenini et al. 1984; Cenini et al. 1988b; Han et al. 1987; Han et al. 1989) and iron (Alper and Paik 1978; Andrews and Kaesz 1979; Des Abbayes and Alper 1977; Landesberg et al. 1972; Williams et al. 1987) catalysts. However, it should be noted that we later proved by *in situ* spectroscopic techniques and kinetic experiments that the proposed imido clusters play no role in the reduction/carbonylation reactions of nitroarenes (Cenini and Ragaini 1996; Ragaini and Cenini 2000; Ragaini et al. 1999b; Ragaini et al. 1995). Actually, in the case of ruthenium, no cluster plays a role at all and only mononuclear species are involved in the reaction under the real reaction conditions. Although an active role of imido clusters in cyclization reactions such as those here discussed has never been experimentally disproved, the results mentioned above make it very unlikely their involvement in the main reaction pathway. Formation of mononuclear imido complexes should be more energetically demanding. Although such complexes have been proposed in several cases to be the active aminating species, no experimental evidence has ever been provided to support this proposal and results accumulated during the years rather support an active role of nitrosoarenes in most reactions (*vide infra*), thus avoiding the need for a complete deoxygenation of the nitroarene before the C-H activation step.

Anilines are always formed as byproducts in all cyclization reactions. In general, any time some water is present, it appears that amine formation is faster than any other competing reaction. Thus, water should be carefully excluded from the reaction mixture. However, other solvents such as alcohols can also dehydrogenate under the reaction conditions affording the hydrogen atoms necessary for aniline formation and these solvents should also be avoided. Anilines have shown to be intermediately formed during the synthesis of carbamates with all the most active catalysts known, whereas the direct formation of isocyanates, which can then be trapped by reaction with an alcohol, is either not observed at all or constitute at best a secondary reaction pathway (Ferretti et al. 2014; Ferretti et al. 2015b; Ferretti et al. 2010; Gargulak et al. 1992; Gargulak and Gladfelter 1994a; Gargulak and Gladfelter 1994b; Gasperini et al. 2005a; Gasperini et al. 2007; Gasperini et al. 2005b; Ragaini and Cenini 2000; Ragaini et al. 1994; Ragaini et al. 2003b; Ragaini et al. 2000; Ragaini et al. 2004b; Ragaini et al. 2009a; Ragaini et al. 1999b; Ragaini et al. 1997). However, in fine chemicals synthesis, anilines have clearly been shown to be intermediates in the main reaction pathway only in the case of the formation of imines (Schiff bases) by reaction of nitroarenes with aldehydes in the presence of CO (eq. 1).



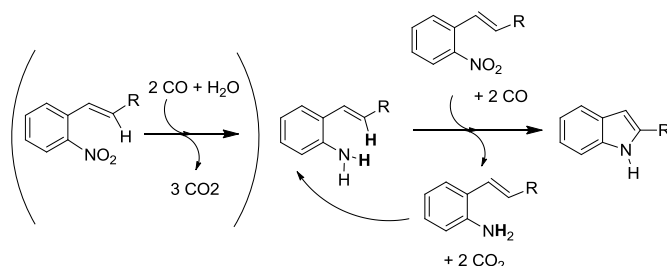
The reaction was known to be catalyzed by rhodium and palladium complexes and, less efficiently, by other metals (Akazome et al. 1992; Iqbal 1972). A nitrene complex had been proposed to react with the aldehyde to give an intermediate nitron (Path A in Scheme 4). As a support, an independently synthesized nitron had been shown to be deoxygenated by CO under the reaction conditions.



Scheme 4. Alternative reaction pathways for the synthesis of Schiff bases from nitroarenes and aldehydes

However, we showed that both with rhodium and palladium catalysts the kinetics of the reaction is cleanly first order in added water (a few microliters)(Ragaini and Cenini 1999). The intercept when no water was added (10 μ L water in 10 mL dichlorobenzene, 20 μ L water in 10 mL dioxane) is compatible with the amount of water that may be present as an impurity even in carefully dried solvents, considering that traces of water are also present in the CO gas. The first order kinetics in water clearly indicates that a different pathway (path B in Scheme 4) is operating. Water acts as a catalyst in this cycle. Note that Schiff base formation only occurs to a partial extent if aniline and the aldehyde are reacted under the same experimental conditions because in this case water accumulates and hydrolyzes the formed imine over certain concentrations.

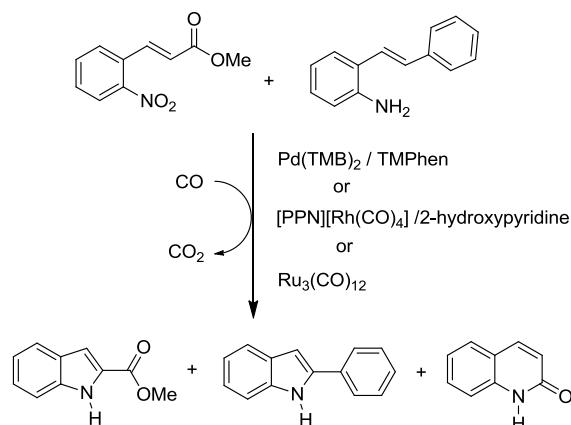
The possible involvement of anilines as intermediates was also investigated in the context of the synthesis of indoles and different types of heterocycles (Ragaini et al. 1999c). In general, such a test can be tricky. Indeed, cyclization of an *ortho*-aminostyrene should generate a heterocycle with a saturated five-membered ring and an analogous outcome should occur in other cases. However, if a nitroarene is present, this may act as an oxidant and cause the aromatization of the formed ring, possibly while this is still bound to the metal. The general process is shown in Scheme 5, where the hydrogen atoms shuttling from the nitro to the amino group have been evidence in bold.



Scheme 5. Possible role of amines as intermediates in the synthesis of indoles

A trace amount of water may be sufficient to generate a “catalytic” amount of aminostyrene, which would then be regenerated during the process, as it occurs in the synthesis of imines. This reaction scheme could not be sustained in the absence of a reagent able to act as an oxidant. Thus, failure to obtain the desired heterocycle when starting from an aminostyrene would not imply that aminostyrenes cannot be intermediates when a nitroarene is employed as substrate. The only way to check if a reaction scheme as that depicted above is operating or not is to run a reaction using as substrates a mixture of a nitrostyrene and an aminostyrene bearing different substituents on the aryl ring or the double bond, so that the substrate originating the indole product can be traced back.

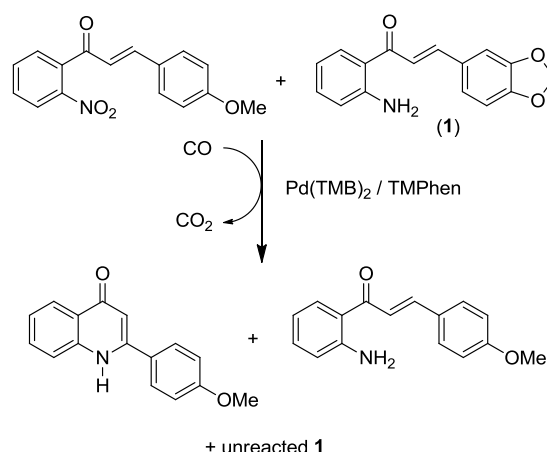
Three different, previously reported catalytic systems for the synthesis of indoles from *o*-nitrostyrenes were tested: one employing $\text{Pd}(\text{TMB})_2$ in the presence of TMPhen (TMB = 2,4,6-trimethylbenzoate, TMPhen = 3,4,7,8-tetramethyl-1,10-phenanthroline) (Tollari et al. 1994a), one employing $[\text{PPN}][\text{Rh}(\text{CO})_4]$ in the presence of 2-hydroxypyridine (PPN = $(\text{PPh}_3)_2\text{N}^+$) (Ragaini et al. 1996), and one employing $\text{Ru}_3(\text{CO})_{12}$ (Crotti et al. 1986) as catalysts. The substrates used were methyl-2-nitrocinnamate and 2-aminostilbene (Scheme 6).



Scheme 6. Possible involvement of amines as intermediates in the synthesis of indoles

Nitroarene conversion was always complete, whereas the amine was only partly consumed. However, in all cases 2-phenylindole was also formed. In the cases of the palladium and ruthenium catalysts, only a very small amount of the latter product was obtained (3-5 mol% with respect to 2-carbomethoxyindole), pointing to a negligible, though existing, role of a reaction pathway passing through amine formation. However, in the case of the rhodium catalyst, the mol ratio 2-phenylindole/2-carbomethoxyindole was 0.34. This indicates that even if the main pathway does not involve amine as an intermediate, a secondary and competitive pathway does and its contribution to the reaction outcome is significant. Some amine is necessarily generated from the nitroarene, but in this specific system it seems to be mostly consumed by a competitive cyclization reaction affording a quinolone as the product.

The same kind of test was also applied to another cyclization reaction, the synthesis of quinolones from 2-nitrochalcones. We had previously reported this kind of cyclization using $\text{Ru}_3(\text{CO})_{12}$ in the presence of a chelating Schiff base, Tol-BIAN (Tol-BIAN = *bis*-(4-tolylimino)acenaphthene, see also Scheme 9) as the catalytic system (Tollari et al. 1994b). Under these conditions, some dihydroquinolone was also formed, that is very likely to derive from a Michael condensation of an intermediately formed amine. However, it was later shown that the $\text{Pd}(\text{TMB})_2 / \text{TMPhen}$ system mentioned above is selective for the unsaturated product. Thus, the latter was chosen for a mechanistic investigation. In this case (Scheme 7), the result was clear-cut. No quinolone or dihydroquinolone derived from the amine was observed at the end of the reaction and the amine was recovered unaltered, whereas the expected quinolone and some amine were obtained from the nitrochalcone.



Scheme 7. Possible involvement of amines as intermediates in the synthesis of quinolones

Thus, it is clear that amines are not intermediates in this reaction, at least when a palladium catalyst is employed.

It is worth mentioning that the synthesis of quinolones from *ortho*-nitrochalcones was the first cyclization reaction employing a nitroarene as the reactant to produce a six membered ring efficiently. Previously, only five

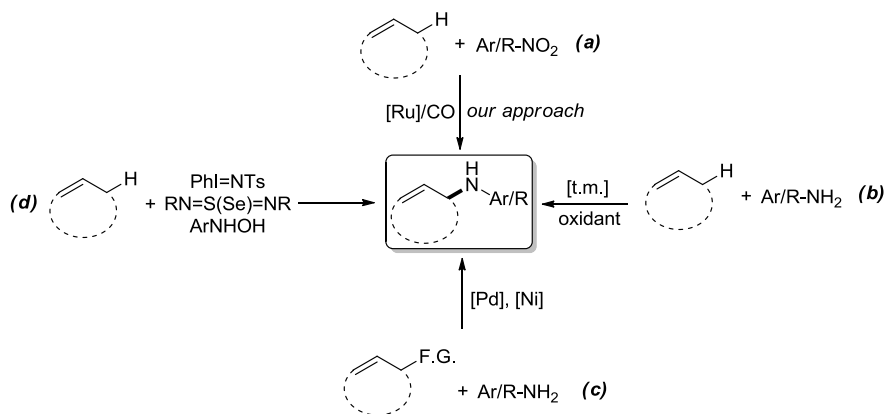
membered rings had been obtained and attempts to get six membered rings either had produced a five membered ring after an isomerization or had generated only trace amounts of the desired heterocycle (Bassoli et al. 1994; Bassoli et al. 1989).

Given the limited or null role that imido complexes and amines appears to play as intermediates in the cyclization reaction, the question of the relevant intermediate arises more urgently. Nitrosoarenes were proposed to be the relevant aminating species when the deoxygenation of the nitro group was performed by triethylphosphite as early as 1965 (Sundberg 1965) and in the case of a metal/CO combination in 1994 (Bassoli et al. 1994), but without providing any experimental evidence in both cases. Experimental evidence for their involvement in the cyclization of *ortho*-nitrostyrenes to indoles and of *ortho*-nitrochalcones to quinolones was later obtained, based on the fact that some *N*-hydroxy-indoles and *N*-hydroxy-quinolones could be observed in the final reaction mixtures under the proper experimental conditions, low temperature and short reaction times (Tollari et al. 2000). When the reaction time was prolonged, the isolated amount of *N*-hydroxy compounds decreased and that of the corresponding N-H heterocycles increased. This supports the view that they are not side product of the reaction, but real intermediates, which are deoxygenated by CO upon further reaction.

More recently, the cyclization reactions of *ortho*-nitrostyrenes to indoles and *ortho*-nitrobiphenyls to give carbazoles have been investigated by theoretical calculations (Davies et al. 2004; Leach et al. 2005; Vidhani and Krafft 2015). The conclusion is that both processes should be possible even in the absence of a metal, although an involvement of a metal and/or a base was considered to possibly play a role in promoting a hydrogen shift necessary to complete the reaction. That a possible nitrostyrene intermediate should cyclize very easily is supported by the fact that compounds of this class have never been isolated or even observed and that oxidation of an *ortho*-hydroxylamino-azastyrene derivative directly afforded the corresponding aza-*N*-hydroxyindole even at 0 °C: the supposed nitroso intermediate was not observed (Kuzmich and Mulrooney 2003). Thus, it is very likely that nitrostyrenes are the intermediates leading to the cyclization step in the indole synthesis and that this step may occurs outside the coordination sphere of the metal. An active role of nitroso intermediates is also very likely in other reactions, although the conclusion that these reactions always occur outside the coordination sphere of the metal may not be general. For example, *ortho*-nitrosobiphenyl is a stable molecule, at least at room temperature, so that a role of the metal in facilitating its conversion to *N*-hydroxycarbazole should not be disregarded without an experimental evidence. Nitrosoarenes are also surely involved in some *inter*-molecular cyclization reactions that will be discussed in the next paragraphs. Here, again, an active role of the metal in the cyclization step seems not to be required in some cases, but appears to be involved in others. More research is needed in this area to reach conclusions that are more general.

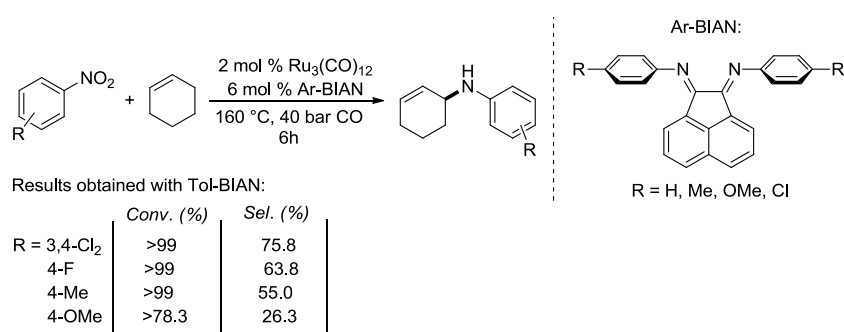
Synthesis of allylamines

Allylic amines are compounds of primary relevance owing to their broad application in many fields (Grange et al. 2016). At the time of our preliminary investigations, the only methods for their production involved the use of pre-functionalized allylic substrates and amines (catalyzed by Pd or Ni complexes, path **b** in Scheme 1) or the employment of nitrene sources and aryl hydroxylamines (path **d**, Scheme 1) both under stoichiometric or catalytic conditions. Only one isolated example of direct functionalization starting from an amine under oxidative conditions was reported until 1996 (path **b**, Scheme 8)(Srivastava and Nicholas 1996). As the consequence, the development of synthetic procedures involving the direct C-H functionalization of olefins with readily available starting materials (such as nitro compounds) was a topic of relevant interest.



Scheme 8 Possible syntheses of allylic amines

The breakthrough in the field was made in 1996 when our group reported the first example of amination reaction of an unactivated olefin with aromatic nitro compounds (path **a**, Scheme 8)(Cenini et al. 1996). This was also the first *inter-molecular* C-N bond forming reaction using a nitroarene as the aminating species. $\text{Ru}_3(\text{CO})_{12}$ in combination with chelating N-donor ligands of the Ar-BIAN family was able to catalyze the reaction between substituted nitroarenes and cyclohexene used as reaction medium (Scheme 9).

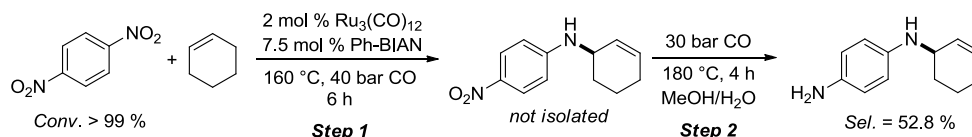


Scheme 9. Synthesis of allylic amines from nitroarenes and unactivated olefins (only cyclohexene derivatives are shown)

By using this protocol, nitro compounds bearing electron-withdrawing groups (EWG) or mildly electron donating groups (EDG) were smoothly converted with good selectivities, with EWG affording better selectivities. However, in the case of 4-methoxynitrobenzene, a complete conversion was not achieved that was even accompanied by a poor selectivity into the desired product. The predominant side products were found to be the corresponding anilines whose production can be partly due to the presence of adventitious water into the reaction mixture. Indeed, the catalytic system based on $\text{Ru}_3(\text{CO})_{12}$ /Ar-BIAN is able to catalyze this transformation very efficiently (Ragaini et al. 2001b; Ragaini et al. 1993; Viganò et al. 2010). Cyclohexene dehydrogenation can also contribute the hydrogen atoms required for the formation of aniline. Indeed, a careful GC-MS analysis of the volatile fraction after the end of the reaction allowed to evidence the presence of benzene and cyclohexadiene. The same two products were not present in the starting solvent.

A closer examination of the electronic effect in the ligand revealed that a regular trend cannot be recognized and no correlation was observed between either the conversion or the selectivity and the σ -Hammett of the R groups in the *para* position of the aryl moiety in Ar-BIAN. In fact, although the conversion seems to be independent from the electronic situation of the ligand, the selectivity in allylic amine follows the order $\text{H} > \text{Me} > \text{OMe} > \text{Cl}$. Concerning the scope of the olefins, cyclopentene, cyclooctene and α -methylstyrene provided very good conversions and moderate to good selectivities into the desired allylic amine. Screening of other ligands revealed that the use of Ar-BIANs was crucial to direct the transformation towards the desired product. In confirmation of this, TMPhen or DPPE (1,2-bis(diphenylphosphino)ethane) showed poor selectivities (< 26 %) in the allylic amine, aniline being the principal product.

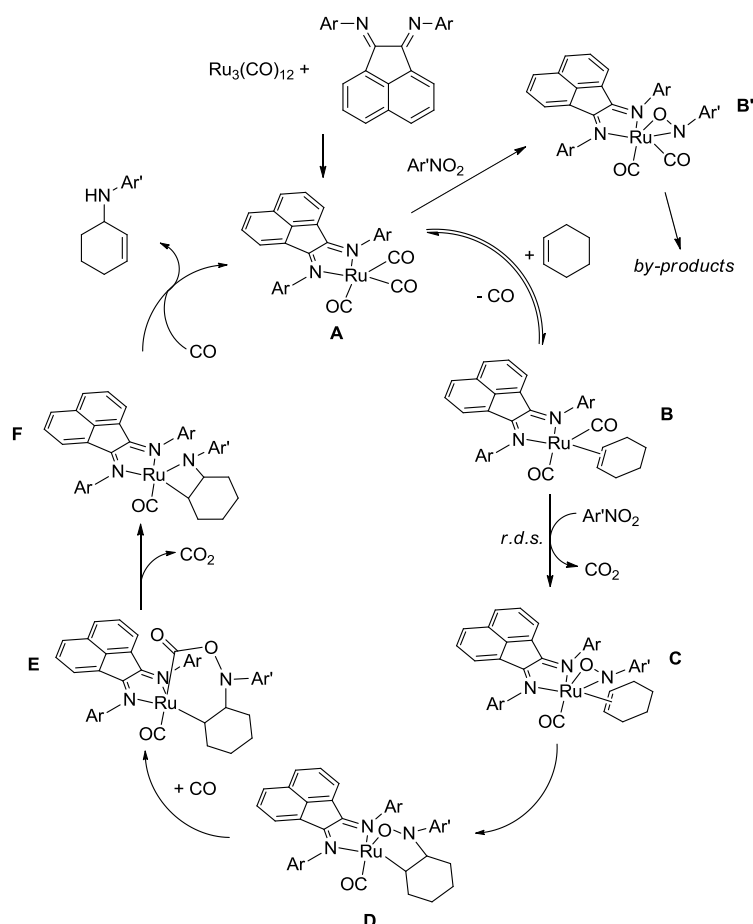
As previously mentioned, nitroarenes bearing EWG gave the best results both in terms of conversion and selectivity. On the contrary, strongly EDG, such as the methoxy group, led to a very poor reaction rate. Since the first step of the reaction is a single electron-transfer (SET) from the ruthenium complex to the nitroarene (*vide infra*), EDG on the latter tends to disfavor the process. However, allylic amines bearing EDG and especially amino groups on the aryl ring are of primary importance not only as such but also because of the possibility of further functionalization. As an example, aryl amines are starting point for the preparation of diazonium salts that exhibit a wide range of useful reactions. Our approach for the preparation of the desired 4-amino substituted allylic amine was based on two peculiar kind of reactivity (Ragaini et al. 2004a). Firstly, the allylic amination of 1,4-dinitrobenzene selectively proceeds until the stage of the monoaminated product because the formation of an allylamine group on the aryl ring deactivates the second nitro group. Secondly, as previously mentioned, the $\text{Ru}_3(\text{CO})_{12}/\text{Ar-BIAN}$ couple is able to efficiently catalyze the reduction of nitro compounds to the corresponding aryl amines in the presence of CO and H_2O (*vide supra*). This is an easier reaction with respect to the formation of allylic amines and also proceeds at high rate with deactivated nitroarenes. Integrating this two features, we developed a one-pot two-step protocol in which in the first stage the allylic amine still bearing the unaffected nitro group was produced with good selectivity (Step 1, Scheme 10). Subsequently, the simple addition of $\text{MeOH}/\text{H}_2\text{O}$ to the reaction mixture led to the formation of the desired aniline under similar reaction conditions using the same catalytic system (Step 2, Scheme 10). Noteworthy, the second step proceed with complete conversion and selectivity thus enabling the synthesis of the final compound in 53 % yield. This clearly indicates that the catalytic systems is still active after the amination step.



Scheme 10. Two-step strategy for the synthesis of 3-(4-aminophenyl)cyclohexene

As an attempt of making enantioselective the formation of the allylic amine, enantiomerically pure *bis*-oxazolines were employed as ligands instead of Ar-BIANs (no examples of chiral and enantiomerically pure BIAN complexes existed at the time). Unfortunately, the activities were poor with respect to the Ar-BIAN counterparts and low allylic amines selectivities were achieved. As the consequence, no further investigations were made.

The reaction mechanism of the presented transformation was extensively investigated (Ragaini et al. 1999a). First of all, the reaction between $\text{Ru}_3(\text{CO})_{12}$ and Ar-BIANs was studied, evidencing that a monomeric monoligated Ru complex was formed (**A** in Scheme 11). The reaction proceeds well with 2,6-*i*-Pr₂C₆H₃-BIAN, Ph-BIAN and Tol-BIAN although only in the first case the complex can be isolated in a pure form. Furthermore, kinetic studies revealed a first-order dependence of the catalytic reaction rate with respect to nitrobenzene and olefin concentrations. However, in the latter case an olefin-independent term was present (non-zero intercept). These evidences not only indicate that nitroarene activation is the rate-determining step of the reaction, but even that a pre-equilibrium between the $\text{Ru}(\text{CO})_3(\text{Ar-BIAN})$ (**A**) and $\text{Ru}(\text{CO})_2(\text{cyclohexene})(\text{Ar-BIAN})$ (**B**) complexes before the r.d.s exists. Both species are able to react with nitrobenzene. However, **B** reacts faster. The resulting species is a η^2 -coordinated nitrosoarene complex of type **C**. It should be noted that even complex **A** is able to react with nitroarene (even at room temperature) affording the $\text{Ru}(\text{CO})_2(\text{Ar-BIAN})(\eta^2\text{-ONAr})$ complex **B'**. However, no allylic amine could be obtained by reaction of **B'** with cyclohexene, demonstrating that it is not a reaction intermediate in its synthesis and can only afford by-products. The reaction very likely proceeds with the insertion of the C=C double bond into the Ru-N bond, leading to the formation of a 5-membered metallacyclic intermediate **D**, which is able to insert a second equivalent of CO, generating intermediate **E**. The latter, after CO_2 elimination, is converted into **F**, which finally produces the desired allylic amine, restoring the starting $\text{Ru}(\text{CO})_3(\text{Ar-BIAN})$ complex.



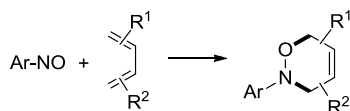
Scheme 11. Reaction mechanism for the Ru/Ar-BIAN catalyzed allylic amination of olefins by nitroarenes

In order to discriminate between the actual aminating agents, several competitive experiments were performed. The results indicate that the allylic amine derives from a Ru-ligated nitrosoarene, thus excluding any role of possible free nitroso species. Moreover, if a mixture of a nitroarene and an aniline bearing different substituents is employed as substrate, only the allylic amine derived from the nitroarene is obtained, barring any possible intermediate role of aniline as the aminating agent.

In the original papers, other catalytic systems had been tested, including the $\text{Pd}(\text{TMB})_2/\text{TMPhen}$ one previously mentioned, but much poorer results were obtained. However, in the following years, we showed that most nitroarene reduction/cyclization reactions originally reported with other metals, could also be performed more efficiently by palladium/phenanthroline systems (see both previous and next paragraphs). Thus, the low selectivity observed in the allylic amination became surprising and we recently reinvestigated the use of palladium in this reaction (El-Atawy et al.). Results could be improved somewhat with respect to the previously obtained ones, but despite several ligands (including monodentate nitrogen ligands and heterocyclic carbenes) and palladium precursors were employed, the best yield in allylic amine was 23 %, which is much lower than that achievable with the use of the ruthenium/Ar-BIAN system. Thus, at least at the moment, the latter remains a unique catalyst for this reaction.

Synthesis of oxazines and pyrroles

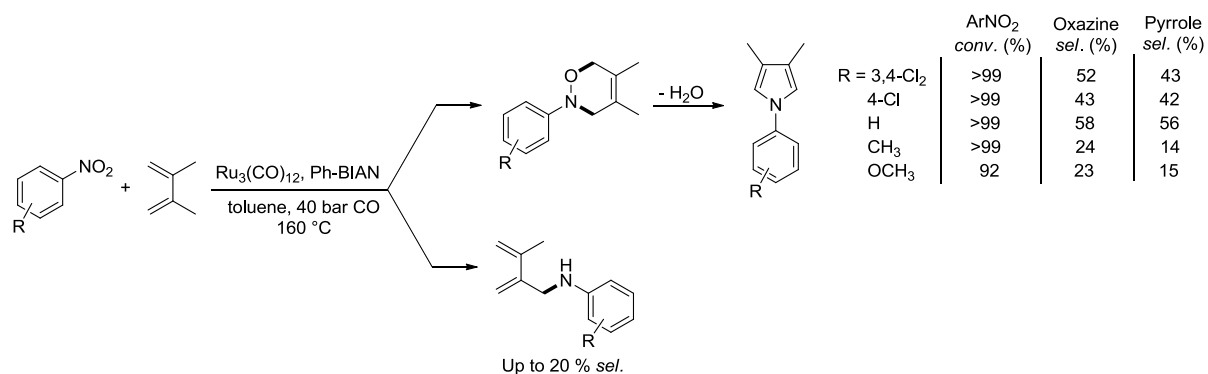
A class of oxazines, namely 3,6-dihydro-1,2-2*H*-oxazine, can be produced by a hetero-Diels-Alder ([4+2] cycloaddition) reaction between nitrosocompounds and substituted dienes (Scheme 12)(Adam and Krebs 2003).



Scheme 12. Hetero Diels-Alder reaction between a nitrosoarene and a conjugated diene.

Given the high efficiency with which such a condensation occurs, it has long been used as a test for the formation of free nitrosoarenes during reactions in which these reagents were not present since the beginning. For example, some iron and molybdenum complexes catalyze the allylic amination of olefins by hydroxylamines and the formation of a nitrosoarene intermediate, either free or coordinate, was surmised. Use of dimethylbutadiene as a substrate allows in principle to distinguish these possibilities. If the reaction product is an oxazine, the intermediate formation of a free nitrosoarene is strongly implicated, whereas if the allylic amine is the product, the species responsible for the amination reaction must be different (Johannsen and Jorgensen 1995; Srivastava and Nicholas 1994).

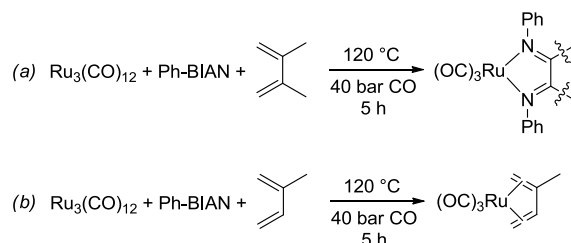
We also initially employed a diene as the olefin for mechanistic purposes while studying the previously mentioned $\text{Ru}_3(\text{CO})_{12}/\text{Ar-BIAN}$ catalytic system for the allylic amination of olefins from nitroarenes (Ragaini et al. 1999a). The results showed a complex situation in which both the oxazine and the allylic amines were produced, indicating that the allylic amination does not proceed by free nitrosoarenes and the same may be true for formation of oxazines, although it is not possible to exclude completely that some free nitrosoarene is also involved in the latter process. In addition, *N*-arylpyrroles were detected as byproducts deriving from a thermal dehydration of the Diels-Alder adducts (Scheme 13)



Scheme 13. Formation of allylic amines, oxazines and pyrroles from nitroarenes and dimethylbutadiene.

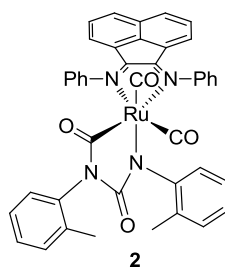
That was the first case in which oxazines and pyrroles could be obtained starting from a nitroarene and we immediately realized that the reaction had a synthetic potential independent of its mechanistic significance. Thus it was investigated more in detail in a dedicated paper (Ragaini et al. 2001a). Screening of the reaction conditions revealed that the selectivity into the Diels-Alder adduct and the *N*-arylpyrrole could be directed simply by varying the reaction temperature, whereas the amount of allylic amine (11-15 % in the case of nitrobenzene) was little sensitive to this parameter. In fact, at 120 °C the oxazine is rather stable and no pyrrole was detected at all. However, if the reaction was conducted at 200 °C, pyrrole was quantitatively formed from the corresponding oxazine. EWG on the nitroarenes led to similar results (in terms of both conversion and selectivities) with respect to the unsubstituted nitrobenzene. On the contrary, EDG tend to decelerate the reaction lowering the selectivities in the desired products. Further studies on the use of other dienes, revealed that 1,4-diphenylbutadiene and cyclohexadiene led to unsatisfactory results. It is known that the formation of the hetero Diels-Alder adduct of nitrosobenzene with these dienes is reversible. Since adduct formation is entropically disfavored, such compounds only form to a very low extent at the temperatures required for the nitroarene reduction to proceed. On the other hand, isoprene (2-methyl-1,3-butadiene) smoothly reacted with 4-chloronitrobenzene yielding only one of the two possible regioisomers, that with the methyl group closer to the nitrogen atom.

In the same paper, we focused our attention on the identification of catalytically inactive species (deactivation pathways) and the resting state of the catalytic system. Concerning the former case, two parallel experiments showed that if isoprene was employed as diene instead of 2,3-dimethyl-1,3-butadiene, $\text{Ru}(\text{CO})_3(\eta^4\text{-isoprene})$ was formed under catalytic conditions in the absence of nitrobenzene. On the contrary, when 2,3-dimethyl-1,3-butadiene was employed, $\text{Ru}(\text{CO})_3(\text{Ph-BIAN})$ was almost exclusively formed. Further experiments revealed that $\text{Ru}(\text{CO})_3(\eta^4\text{-isoprene})$ is much less reactive towards nitrobenzene than $\text{Ru}(\text{CO})_3(\text{Ph-BIAN})$.



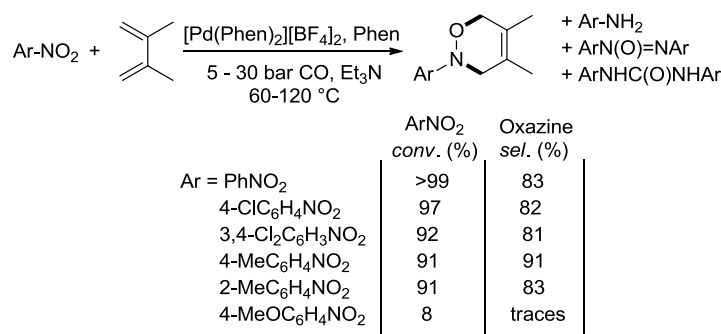
Scheme 14. Ruthenium complexes observed under high CO pressure

Moreover, when *o*-methylnitrobenzene was employed, at the end of the reaction complex **2** (Scheme 15) was formed. The latter complex showed catalytic activity when reacted with 3,4-dichloronitrobenzene and 2,3-dimethyl-1,3-butadiene, giving selectivities comparable to those observed in the case of $\text{Ru}_3(\text{CO})_{12}/\text{Ph-BIAN}$, but the activity was lower than usual. This means that **2** is not a productive intermediate in the transformations, but can re-enter the catalytic cycle. Thus, it can be considered a resting state of the catalyst.



Scheme 15. Resting state of the ruthenium/Ph-BIAN catalytic system

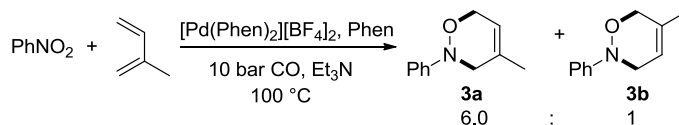
In 2003, we reported that the formation of oxazines and *N*-arylpyrroles from nitroarenes and dienes is also catalyzed by Pd/1,10-phenanthroline (Phen) complexes (Ragaini et al. 2003a). Pd/Phen complexes have been extensively used by us and other groups in the reductive carbonylation of nitrobenzene to isocyanates, carbamates, and ureas (Alessio and Mestroni 1984; Alessio and Mestroni 1985; Bontempi et al. 1987; Cenini et al. 1991; Ferretti et al. 2014; Ferretti et al. 2015b; Ferretti et al. 2010; Gasperini et al. 2005a; Gasperini et al. 2003; Gasperini et al. 2007; Gasperini et al. 2005b; Ragaini et al. 2004b; Ragaini et al. 2009a; Ragaini et al. 2011; Wehman et al. 1996a; Wehman et al. 1995; Wehman et al. 1996b). $[\text{Pd}(\text{Phen})_2][\text{BF}_4]_2$ was employed as catalyst in most cases, but other palladium precursors could also be employed. No pyrrole was observed at temperatures up to 120 °C, as for the ruthenium-catalyzed reaction. However, unlikely the latter, no allylic amine was formed under any condition (Scheme 16). The corresponding arylamine, azoxyarene and *N,N'*-diarylurea were detected as side products. THF was the best solvent and the addition of triethylamine was beneficial for the selectivity.



Scheme 16. Palladium-catalyzed oxazine formation

The Pd-based system was found to be much more active and selective than the Ru-based one. In fact, an oxazine selectivity up to 91 % could be achieved using a PhNO₂/Pd ratio of 1250. Note that, in the Ru case, the best selectivity achieved was of 52 % with a substrate/Ru ratio of 30. Moreover, the Pd-catalyzed reaction showed excellent activities and selectivities even at 5 or 10 bar of CO pressure. Consequently, cheap and widespread glass autoclaves can be used instead of metal ones, thus increasing the practical feasibility of the reaction. In addition, a low molar excess of diene is tolerated. As in the case of ruthenium, nitroarenes bearing EWG led to complete conversions and very high oxazine selectivities. On the contrary, EDG such as methoxy group led to very poor conversions (< 8%).

When the reaction of isoprene with nitrobenzene was investigated, a mixture of both possible isomeric oxazines was obtained (Scheme 17), with **3a** strongly prevailing over **3b** (**3a/3b** mol ratio = 6.0)

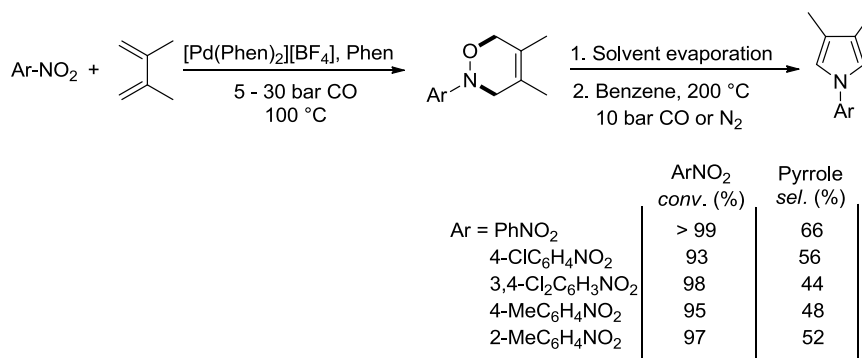


Scheme 17. Isomeric oxazine from isoprene

Exactly the same **3a/3b** ratio was observed when nitrosobenzene was reacted with isoprene in the absence of any metal. This observation, together with the failure to observe the formation of allylic amine under any condition, strongly suggests that in the case of the palladium catalyst the formation of oxazine proceeds by an off-metal condensation of intermediately formed free nitrosoarene with the diene.

From a synthetic point of view, in many cases dienes are more expensive than nitroarenes. Hence, we conducted a reaction with 2 equiv. of nitrobenzene with respect to the diene. A high oxazine yield, 91 %, was obtained, with respect to the diene. This paves the way to the use of expensive or difficult to synthesize dienes. The same outcome would not be possible with ruthenium, as a large excess of the diene is required to get good yields.

As previously mentioned, when the Ru-catalyzed reaction between a diene and a nitroarene is conducted at 200 °C, the oxazine formed is readily converted into the corresponding *N*-arylpyrrole through a dehydration reaction. Unfortunately, when these reaction conditions were applied in the presence of the palladium catalyst, oligomerization products were observed and only traces of the desired pyrrole were detected. This fact can be attributed to the ability of Pd/Phen complexes to catalyze olefins polymerization. Seemingly, under catalytic conditions the active Pd species in the polymerization reaction is formed. In order to circumvent this issue, a one-pot two-step protocol was followed. Firstly, the Pd-catalyzed reaction between the nitroarene and the diene was conducted at 100 °C under 5-10 bar of CO. Subsequently, the solvent (THF) was removed together with the unreacted diene and replaced with benzene or toluene. The autoclave was then recharged with 10 bar of CO or N₂ and heated up to 200 °C. At this stage, the oxazine is converted into the *N*-arylpyrrole without any possible formation of oligomers, with a total selectivity in pyrrole up to 66 % (Scheme 18).

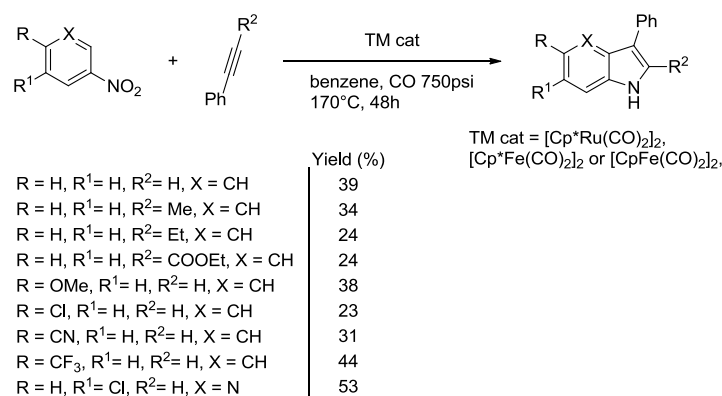


Scheme 18. One pot-two steps protocol for the synthesis of pyrroles from nitroarenes and dienes

Synthesis of indoles

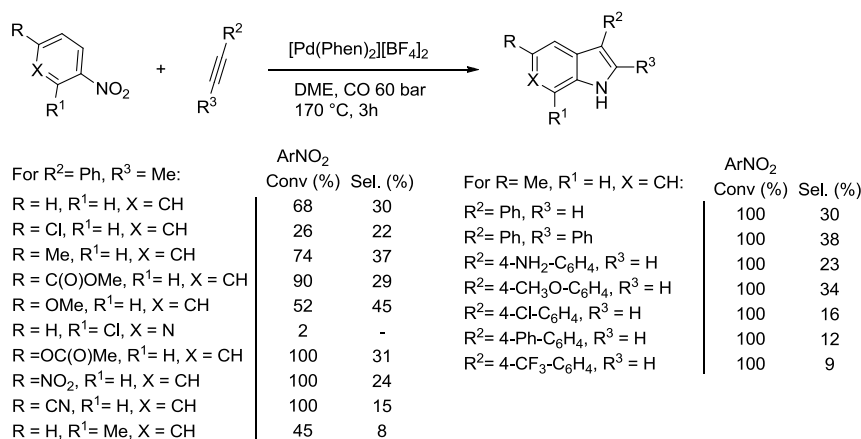
From nitroarenes and alkynes

As mentioned above, the synthesis of indoles from nitro compounds often requires a precursor functionalized in the *ortho* position. An interesting alternative is the reaction of the nitroarene with an external unsaturated C₂ source. Penoni and Nicholas first described such an *inter*-molecular reaction between a nitroarene and an alkyne (Penoni and Nicholas 2002). While trying to synthesize either an allenyl- or a propargylamine from nitrobenzene and 1-phenyl-1-propyne using [CpFe(CO)₂]₂ as catalyst, they noted that 2-methyl-3-phenyl-1*H*-indole formed instead as the major product (Scheme 19). Investigating more deeply the reaction, it was found that the presence of a methyl group on the alkyne is not necessary and the best catalyst is [Cp*Ru(CO)₂]₂. The reaction is regioselective in most cases, affording the 3-phenyl substituted indole but fails when no phenyl substituent is present on the alkyne. A number of groups on the nitroarene are tolerated, but in all cases only fair to moderate yield were obtained. The limit of the reaction resides in the low activity of the system (substrate/metal = 10) and the low turnover frequencies (less than 0.5 h⁻¹ based on converted nitroarene).



Scheme 19. Synthesis of indoles by [Cp*Ru(CO)₂]₂- catalyzed *inter*-molecular reductive cyclization.

A more active catalytic system based on palladium was reported later by our group (Scheme 20)(Ragaini et al. 2006b). Owing to previous experiences on reductive carbonylation of nitroarenes and other cyclization reactions (*vide supra*), [Pd(Phen)₂][BF₄]₂ was used as precatalyst. The reaction of nitrobenzene and phenylacetylene was studied for the optimization of the experimental condition. Although diphenylurea, azo-, azoxybenzene, aniline and dimers of phenylacetylene could be detected as side products, the cyclization reaction is completely regioselective in 3-phenylindole (no traces of 2-phenylindole were detected).



Scheme 20. Synthesis of indoles by [Pd(Phen)₂][BF₄]₂-catalyzed *intermolecular* reductive cyclization.

The reaction can be conducted without large variation in selectivity in the range 130-170 °C, with CO pressures ranging from 20 to 60 bars and best results are obtained in medium polarity solvents (THF or DME = 1,2-dimethoxyethane). Under the best conditions (170 °C, 60 bar in DME), nitrobenzene was completely converted within only 3 h with a catalyst loading of 0.33 mol%, affording a 53 % yield of 3-phenylindole. The catalytic system is 500 fold more active than the [Cp*Ru(CO)₂]₂ based one, although the indole yield was only slightly improved (39% with the Ru system).

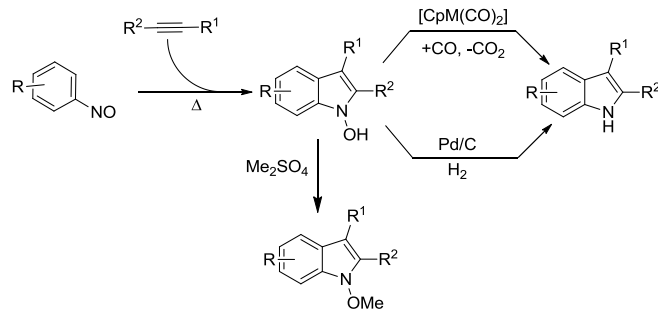
The reaction scope was explored using several differently substituted nitroarenes and alkynes. When alkylalkynes were employed, no indole was observed (although the conversion of the nitroarene was complete). Bis(trimethylsilyl)acetylene and dimethyl acetylenedicarboxylate gave respectively little and no conversion of the nitroarene and the indole was not detected. On the other hand, all the arylalkynes afforded the indole. When an alkyne substituted with two aryl group was employed the reaction was faster whereas if one of the two substituents was an alkyl group it was slowed down. Interestingly, the reaction tolerates several substituents on the aryl ring of the alkyne, including a non-protected primary amino group.

To better understand the effect of the substituent on the nitroarene, a series of reactions of different *para*-substituted nitroarenes with 1-phenylpropyne was carried out. The reaction tolerates both electronwithdrawing and electrondonating groups, but the nitroarene conversion is lower in the presence of the latter. Furthermore, the presence of a methyl in the *ortho* position decreases both the reactivity and the selectivity of the reaction.

It was also noted that prolonging the reaction time after the complete conversion of the nitroarene decreases the product yield due to a partial decomposition of the indole under the reaction conditions. Thus, higher selectivities could be obtained for shorter reaction time with all the alkynes that allow a fast conversion of the nitroarene.

After their initial work on nitroarenes, Nicholas and co-workers also reported that nitrosoarenes react with alkynes even in the absence of a metal catalyst to yield *N*-hydroxyindoles, which can be reduced to indoles in a separate step (Scheme 21)(Penoni et al. 2002). Since the indole selectivities for the annulation of nitro- and nitroso-arenes with alkynes were comparable, it was suggested that the reaction of nitroarenes catalyzed by [CpM(CO)₂] involves an initial reduction to the corresponding nitrosoarenes, which further react with the alkyne through an off-metal process. *N*-Hydroxyindoles can be finally deoxygenated by CO employing the same catalyst used when nitroarenes are the substrates or by catalytic hydrogenation over Pd/C. Formation of *N*-hydroxyindoles during the reaction was deemed responsible for the moderate yields in many cases, as *N*-hydroxyindoles are relatively unstable molecules, prone to dimerization reactions and other unwanted processes. To increase the stability of the product, Nicholas and coworkers performed the uncatalyzed reaction of nitrosoarenes and alkynes in the presence of dimethyl sulfate as an alkylating agent. This way, they obtained *N*-

methoxyindoles with improved selectivities with respect to those achievable in the synthesis of the non-methylated analogues (Scheme 21)(Penoni et al. 2006).



Scheme 21. Synthesis of indoles and *N*-methoxyindoles by uncatalyzed annulation of nitrosoarenes and alkynes.

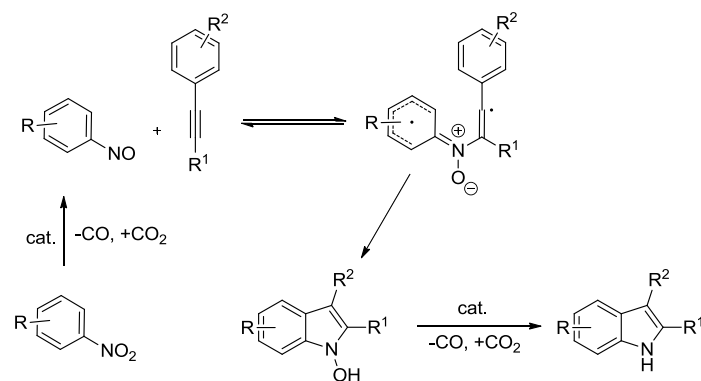
Having in mind the negative effect of the accumulation on *N*-hydroxyindoles in solution, we considered the following:

- 1) No quantitative data are available on the efficiency of different catalysts in the reduction of *N*-hydroxyindoles to indoles by CO, but these compounds resemble hydroxylamines, which are likely intermediates in the reduction by CO/H₂O of nitroarenes. Ruthenium catalysts are much more effective than palladium ones for the latter reaction (*vide supra*), although they are less efficient for the synthesis of indoles.
- 2) *N*-Methoxyindoles may be reduced under the reaction conditions, but dimethylsulfate is surely not compatible with the Pd/Phen catalytic system because it would alkylate the ligand itself. However, a milder alkylating agent, dimethylcarbonate, should be tolerated.

The first strategy was implemented by adding to the reaction mixture Ru₃(CO)₁₂. This cluster was found to be inactive as a catalyst for the cyclization (conversion 5%, indole selectivity 0%) but active to catalyze the reduction of *N*-hydroxyindole (Ragaini et al. 2009b). A ca. 10% increase in the indole selectivity was obtained with 0.33 mol% of triruthenium dodecacarbonyl. The second strategy was also independently tested and allowed for a similar improvement in the selectivity. Worth of note, the two strategies could be employed together and the improvements were almost additive. The effectiveness of the modified catalytic system was shown by synthesizing in just one step the Fluvastatin (a cholesterol-lowering agent) skeleton, namely 3-(4-fluorophenyl)indole, in 71% yield.

Concerning the reaction mechanism, we found that the kinetics is first order in nitroarene and that a linear correlation with a positive slope exists between the logarithm of the kinetic constant and the Hammett σ constant of substituents in the *para* position of the Ar-NO₂ ring. Together, these pieces of information indicate that the r.d.s. is the activation of the nitroarene and the identification of this step as an electron transfer to the nitroarene is supported. If a reaction is performed in the presence of a different aniline, the latter is not included in the product to any detectable extent. Thus, amines are not part even of a minor competitive pathway. The role of the alkyne on the reaction rate is less clear because alkynes surely coordinate to palladium under the reaction conditions. Quite importantly, a correlation between the indole selectivity and a multivariate combination of Hammett polar (σ_p) and radical (σ_{jj}) constants of the substituents on the nitroarene exists.

Taking into account this last piece of information and assuming that the cyclization reaction takes place between the nitrosoarene and the alkyne by an off-metal process, we proposed a mechanism in which the nitrosoarene interacts reversibly with the alkyne through a polarized diradical intermediate (Scheme 22).



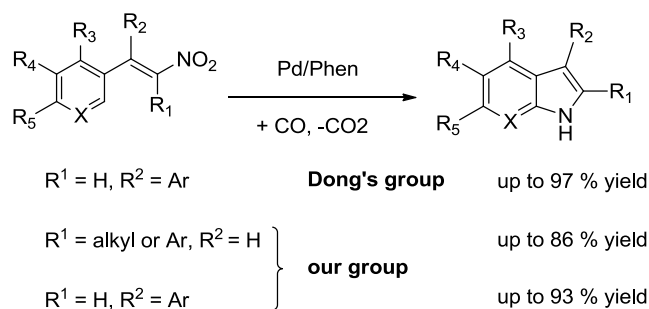
Scheme 22. Reaction mechanism for the reductive cyclization of nitroarenes and alkynes following an off-metal cyclization pathway.

This mechanism explains the requirement for an aryl group on the alkyne; in fact, the aromatic ring stabilizes the radical in the α -position. The polarized diradical character of the intermediate in the cyclization of nitrosoarenes was later confirmed by more detailed mechanistic studies on the uncatalyzed nitrosoarene/alkyne cyclization by the Nicholas and Houk groups (Penoni et al. 2009). Noteworthy, in the uncatalyzed reaction the indole yield is relatively insensitive to the substituents present on the nitrosoarene and, accordingly, calculations showed that polar stabilization effects are less important than radical stabilization ones.

On the contrary, in the case of the palladium/phenanthroline catalyzed reaction of nitroarenes and alkynes, the selectivity is not independent from the substituent on the nitroarene. The polarization that can be deduced (negative charge on the benzylic carbon) from the sign of the Hammett constant in the correlation mentioned above is opposite to that expected for the off-metal mechanism (Scheme 22), suggesting a role of the metal also in the cyclization step (Ragaini et al. 2006b). Unfortunately attempts to isolate possible catalytic intermediates from stoichiometric reactions of palladium/phenanthroline complexes and either nitrosoarenes (Gallo et al. 1999) or alkynes were unsuccessful. At the moment, the exact role of the metal in the cyclization step has not been elucidated.

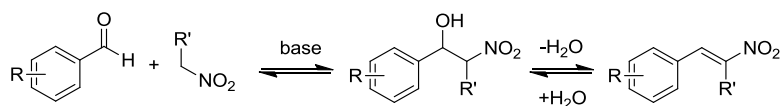
From β -nitrostyrenes

Several years ago, while investigating the use of β -nitrostyrenes as aminating species in the Ru/Ar-BIAN catalyzed allylic amination described in a previous paragraph, we realized that indoles were formed from the nitroalkene instead of aminated products. Palladium/phenanthroline complexes were found to be more active than ruthenium complexes in this cyclization reaction. Before we could develop our system, Dong and co-workers also published similar results. The reaction is synthetically interesting because it does not require the use of substrates bearing an olefin and a nitro group in the *ortho* position (Scheme 23)(Ferretti et al. 2015a; Hsieh and Dong 2009).



Scheme 23. Reductive cyclization of β -nitrostyrenes.

When an aromatic substituent is present in the α position, the reaction can be performed using 2% of catalyst under mild conditions yielding 3-phenylindoles in good to excellent yield (Hsieh and Dong 2009). However, the yield drops dramatically when an alkyl substituent is present in the β position (Ferretti et al. 2015a). Since our work originated from a discovery made using β -methyl- β -nitrostyrene, we employed this compound to optimize the reaction conditions (Ferretti et al. 2015a). Under our conditions, both 3-phenylindoles 2-alkyl- and 2-aryl-indoles could be obtained in high yield using just 1% of catalyst. The important novelty in our report is the possibility of synthesizing indoles from cheap and commercially available compounds. In fact, β -substituted β -nitrostyrene can be straightforwardly obtained from aldehydes and nitroalkanes by a Henry condensation (Scheme 24).

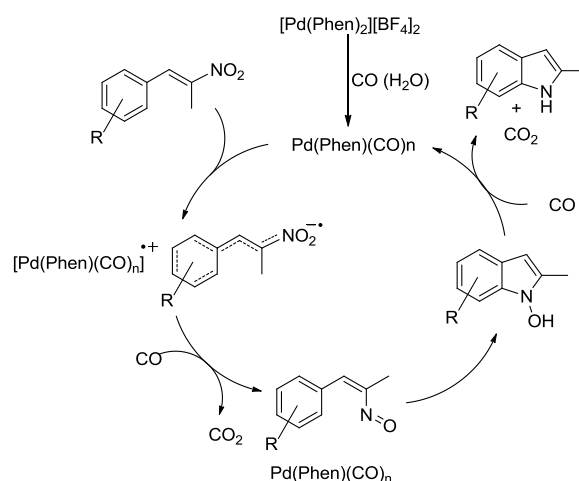


Scheme 24. Henry condensation of nitroalkanes and benzaldehydes.

It is thus clear that the advantage of the reaction over the *intra*-molecular cyclization of *ortho*-nitrostyrenes is the possibility of obtaining indoles in just two steps avoiding difficult pre-functionalization of the substrate. With respect to the *inter*-molecular cyclization of nitroarenes and alkynes, an advantage is the applicability of the reaction to the synthesis of indoles variously substituted in the 2 and 3 positions, rather than just 3-aryl substituted indoles.

The scope of the reaction is quite broad since the presence of both electronwithdrawing groups and electron donating groups is well tolerated. Noteworthy, azaindoles can also be obtained. The reduction of the nitro group is slightly slower in the presence of strongly EDG such as methoxy and is almost completely inhibited by a diethylamino group. A limit of the method is the need for a substituent either in the α or the β position of the styrene. In fact, β -nitrostyrene preferentially undergoes polymerization rather than yielding the indole.

On the base of previous studies on the reductive carbonylation of nitro compounds (*vide supra*), we proposed a reaction mechanism (Scheme 25).



Scheme 25. Proposed reaction mechanism for the reductive cyclization of β -methyl- β -nitrostyrene

The first step of the cycle is the formation of a radical anion by a single-electron transfer from the metal to the nitroalkene followed by the formation of a nitrosoalkene, which is the aminating species. As for the previously described reductive cyclization reactions, *N*-hydroxyindole is intermediately formed and then reduced by carbon monoxide to yield indole.

The difference in reactivity between α -aryl- β -nitrostyrenes and β -alkyl- β -nitrostyrenes can be explained by the different reduction potentials of the two substrates and by the formation of the radical anion. This is favored by the presence of an extended conjugated π system as determined by the presence of an aryl in α position. In addition, the easy rotation of the N-containing group around the double bond during the formation of the radical anion explains why indoles could be obtained in good yields even from *trans*- β -nitrostyrenes and the higher selectivity obtained for α -phenyl- β -nitrostyrenes, for which the chances of proper orientation of the aminating species and phenyl ring are maximized.

Conclusions

The reduction of organic nitro compounds by carbon monoxide as a tool to prepare nitrogen heterocycles is a field that has slowly evolved during the years. Apart from a few pioneering reports, a real start of this chemistry occurred in the '80s and was mostly based on the use of rhodium and ruthenium compounds, especially carbonyl clusters. Reaction conditions were harsh and yields usually moderate or low. The introduction of palladium/phenanthroline complexes as catalysts in the '90s by the group of Cenini, from which our present group originates, allowed to decrease the reaction temperature and pressure and to achieve higher selectivities in the desired products. Palladium/phenanthroline complexes are almost exclusively used as catalysts in the recent literature. Many substrate types and combinations are still to be explored and new reactions are developed right now in our laboratories. Although this account mainly focusses on our contributions to the field, it must be recognized that other scientists, whose names can be found in the references, also contributed with major advancements and many of our results would not be possible without the inspiration originated from their works.

Despite the advantages the reactions here discussed have in terms of atom economy and ease of purification of the products, they have not become of general use. One limitation is surely the need for the use of pressurized carbon monoxide, which requires high-pressure CO lines not available in most laboratories. Our group is developing the use of other molecules that can liberate CO under the reaction conditions, accompanied by non-toxic and easily separable coproducts. Hopefully, these modifications will allow a more widespread use of this chemistry.

Acknowledgements

First of all, we would like to thank Prof. S. Cenini, who introduced us to this fascinating field. Prof. E. Gallo and Prof. A. Caselli are also thanked for the help they provided over several years. Finally, we want to thank all the students who contributed to the development of the chemistry discussed in this review and whose names can be found in the references.

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