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Authors: Francesco Ferretti, Doaa R. Ramadan, and Fabio Ragaini

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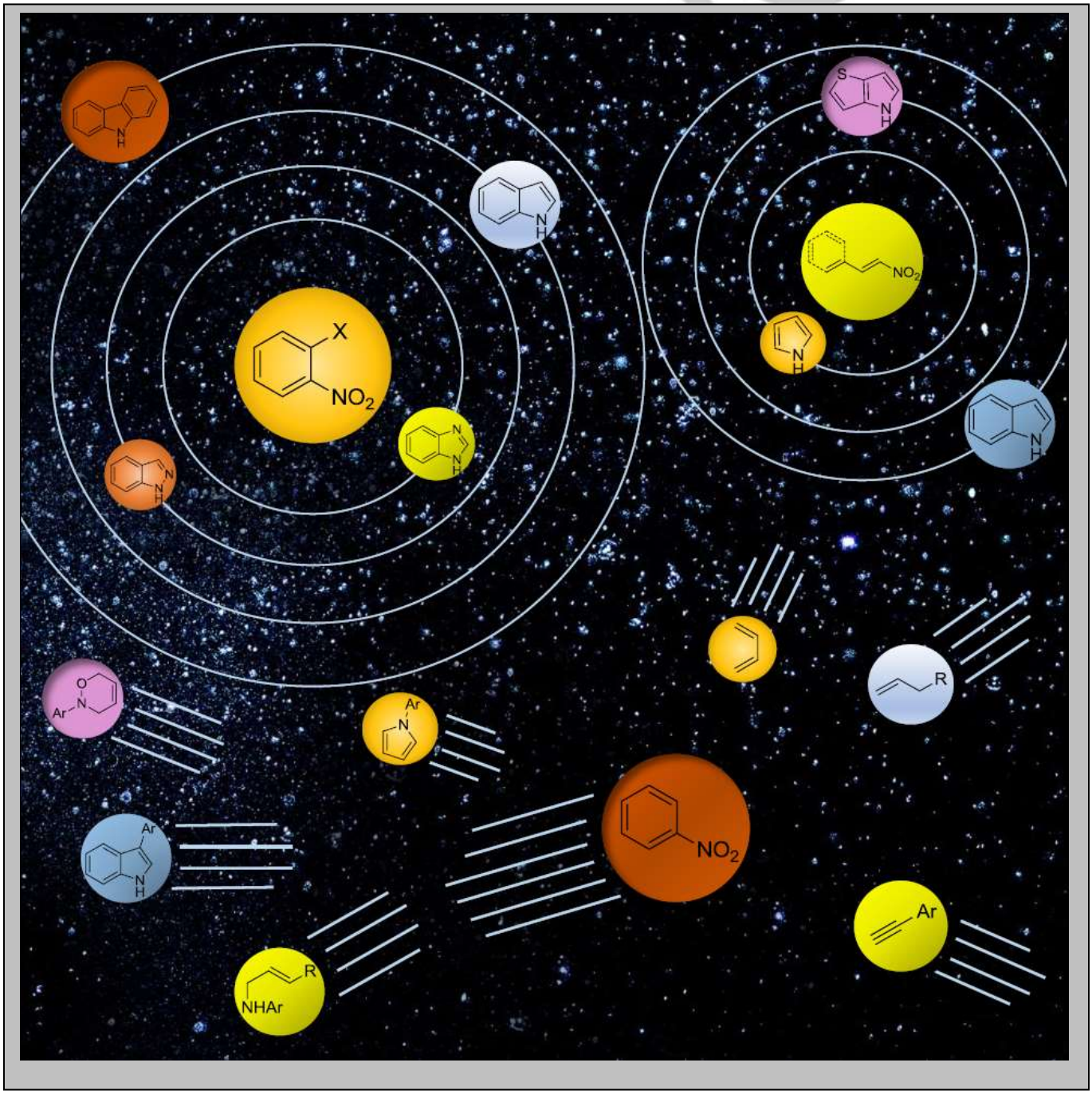
Transition Metal Catalyzed Reductive Cyclization Reactions of Nitroarenes and Nitroalkenes

Francesco Ferretti,[a] Doaa R. Ramadan,[a] and Fabio Ragaini*[a]



Abstract: Nitroarenes are the entry point for the production of most nitrogen-containing aromatic compounds. Thus, any transformation that leads directly from them to the final product allows saving one or more synthetic steps. This review deals with homogeneously catalyzed reactions leading to the formation of *N*-heterocyclic compounds from nitroarenes or nitroalkenes in one pot. Reactions that lead to the intermediate formation of amines are not considered. Carbon monoxide is the most often employed reductant because it allows selective reactions, is cheap, and only produces CO_2 as stoichiometric byproduct. However, the difficulty in handling pressurized CO has stimulated in recent years the development of CO-surrogates, that is molecules able to liberate CO during the reaction. The use of phosphines and diols has also been developed in conjunction with molybdenum catalysts. The review focusses in more detail on the literature in the period 2006-2018, but reference to earlier work is made when necessary to put recent results in a more general context.

1. Introduction

N-Heterocycles are key compounds in numerous fields and nitroarenes are the entry point for almost all nitrogen-containing aromatic compounds. Thus, it is obvious that the use of nitroarenes to synthesize *N*-heterocycles in one pot has attracted much interest. In several cases, the nitroarene is first reduced to the corresponding aniline and it is the amino group that is involved in the final cyclization. Such is for example the case of the classical Reissert indole synthesis, where the amino group condense with a keto group, or the Leimgruber-Batcho synthesis, where the keto group is initially protected as vinylamine. Many more examples exist of this kind of reactions, but we decided not to include them in this review in order to focus on the peculiar reactivity of the nitro group and of the reactive intermediates, rather than on the synthetic achievements. In keeping with the idea of one of us (F.R.) that "a good review should look at the future more than at the past", the first part of this review represents a tutorial guide to this class of reactions.

Some of us have previously reviewed the synthesis of fine chemicals by reduction of nitroarenes by carbon monoxide in a book chapter covering the literature up to 1995,[1] a review covering the period 1996-2005,[2] and a personal account, only describing the results obtained in our group.[3] The same field has also been included as part of other reviews with a wider scope.[4-7] The reason for concentrating the attention on the use of carbon monoxide is that it allows the selective reduction of the nitro group in most cases and it is also effective from the point of view of the separation of the products, CO_2 being the only stoichiometric byproduct. Most other reductants, with the exception of dihydrogen and hydrazine, which invariably afford amines as initial products, had only been used as stoichiometric reagents until a few years ago. However, in the last decade some reports have been published in which a molybdenum complex catalyzes the reaction of phosphines or diols with nitroarenes.[8] These cases are included in this review, as well as is the use of CO surrogates, which has also emerged recently.

[a] Dr. F. Ferretti, Dipl. Chem. D. R. Ramadan, Prof. Dr. F. Ragaini*
Dipartimento di Chimica
Università degli Studi di Milano
via C. Golgi 19, 20133 Milano (Italy)
E-mail: fabio.ragaini@unimi.it

Francesco Ferretti studied chemistry at Milan University (Italy), where he earned his PhD in 2013 under the supervision of Prof. Fabio Ragaini. Next, he was a postdoctoral fellow in the same group until 2016, when he moved to the group of Prof. M. Beller at the Leibniz-Institut für Katalyse (Rostock, Germany). He is currently assistant professor at the Milan University. His research interests include homogeneous and heterogeneous catalysis, with a focus on carbonylation and hydrogenation reactions.

Doaa R. Ramadan graduated in 2013 and received her master's degree in chemistry in 2017 from Alexandria University (Egypt). Currently, she is an assistant lecturer at Alexandria University. In 2017, she received a PhD grant from Milan University, and she is currently developing her PhD research under the supervision of Prof. Fabio Ragaini in the field of homogenous catalysis by transition metal complexes.

Fabio Ragaini got his PhD at Milan University in 1991 under the supervision of Prof. Cenini. Apart from a visiting scientist period at The Pennsylvania State University with Prof. Geoffroy, he made his entire academic career within Milan University, eventually becoming a Full Professor in 2008. He is the author of around 120 papers and a monograph most of which in the field of the reduction and carbonylation reactions of nitroarenes.

2. General trends in the reduction of nitroarenes

2.1. Classes of reductants

Nitroarenes can be reduced by a number of reagents. As a rule of thumb, dihydrogen, hydrazine (both in the presence of a catalyst) and hydridic reagents, $NaBH_4$, $LiAlH_4$ and the like, (either in the presence of a catalyst or not) reduces nitroarenes to anilines and the intermediates during the reduction are consumed too quickly to be involved in any cyclization reaction. In order to take advantage of the peculiar reactivity of nitroarenes, reagents that are able to accept an oxygen atom without releasing hydrogen atoms at the same time are required. Apart from carbon monoxide, many other reagents can perform this function. Among these, we evidence phosphites, phosphines, silanes, diboranes and $SnCl_2$ because they can be involved in metal-catalyzed reactions, apart from being usable in the absence of any catalyst. Phosphites and phosphines, in particular, have been widely employed in the absence of any catalyst to promote different cyclization reactions (Cadogan-Sundberg reactions).

2.2. Mode of activation of the nitro group

As far as the activation of nitroarenes by transition metal carbonyl complexes is concerned, the initial step of the reaction has been shown to involve a single electron transfer from the metal to the nitroarene in all the cases in which it has been investigated. These include the use of nickel[9], ruthenium[10-11], iron[12-15], and rhodium[16-18] complexes. No direct evidence for a single electron transfer has been reported in the case of palladium complexes, the metal most widely employed as catalysts, but evidence for radical formation in the activation of nitrosoarenes has been obtained.[19-20] Consequently, only complexes in which the metal is in a low oxidation state, are able to reduce nitroarenes. The literature abounds with mechanistic proposals in which higher oxidation state complexes are shown to activate nitroarenes, usually by nucleophilic attack of the latter to a coordinated CO. However, nitroarenes are among the weakest nucleophiles known and it cannot be stressed enough that not a single piece of experimental evidence has ever been reported for such an activation mode. Specifically, we are not aware of any report in which a palladium(II), ruthenium(II), iron(II), nickel(II) or rhodium(I) complex, either containing coordinated CO or not, have clearly been shown to react with a nitroarene under conditions in which preliminary reduction of the metal to a lower oxidation state can be excluded. Note that this does not apply to those cases in which it is the metal itself, not CO, to act as the reductant by generating a metal-oxo species. Many such cases have been reported, but the reaction is not catalytic, with the exception of some molybdenum complexes that can be employed as catalysts in the presence of phosphines or diols as the end reductants. These cases will be described in a separate section (paragraph 7).

Metal [carbonyl] hydrides are often used as reductants in organic chemistry. However, when nitroarenes are concerned, they are effective only if they are electron-rich enough to act as electron donors, otherwise they are inactive.[21] 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.

The fact that the activation of the nitro group occurs by an electron transfer differentiate it from most other reducible groups such as olefinic, acetylenic, cyano, keto and aldehydic and allows a selective reaction of the nitro group in the presence of all of these groups. The activation of aryl and sometimes even alkyl-halides can involve an electron transfer, but at least in the case of nitroaryl chlorides and bromides, reactions with transition metal carbonyl complexes generally result in the activation of the nitro group and not of the halide. Fewer examples have been reported of reactions involving nitroaryl iodides, so that a general conclusion cannot be reached, but at least in some cases the activation of the nitro group surely prevails.

The activation of the nitro group by an electron transfer bears as a consequence that nitroalkanes, which are much more difficult to reduce than nitroarenes, cannot be employed as substrates in any of the reaction discussed in this review. Nitroalkenes have a reduction potential of the same order of magnitude of that of nitroarenes[22] and have recently been employed as substrates. However, they are less reactive than nitroarenes and a competition experiment in which a nitroarene and a nitroalkene moieties were present on the same molecule resulted in the selective activation of the nitroaryl group.[23]

Note that radical recombination appears to be fast for most if not all reactions described in this review. In the only two cases we are aware of in which a radical trap was added to the reaction mixture,[24-25] the yield of the cyclized product was not altered. However, when the reaction between nitrosobenzene and phenylacetylene was performed in the presence of Galvinoxyl as a radical scavenger, the formation of the main byproduct, azoxybenzene, was largely suppressed.[24] Note that nitrosoarenes are well known radical traps themselves and the inhibition observed suggests that at least under the conditions of that reaction, azoxybenzene formation occurs by a trapping of a nitrosobenzene radical by a second nitrosobenzene molecule.

2.3. Catalysts

In the early literature, ruthenium and rhodium carbonyl clusters ($Ru_3(CO)_{12}$, $Rh_4(CO)_{14}$, $Rh_6(CO)_{16}$) were mostly employed as catalysts for the reductive cyclization of nitroarenes by CO. However, forcing conditions were usually needed to effect the reaction. Several ligands and additives have been then discovered that allow for the use of milder reaction conditions (see later the dedicated paragraphs). In the last twenty years, palladium complexes have been mostly employed and allowed for higher selectivities to be achieved under milder experimental conditions.

In most cases, it appears that the identity of the metal complex initially added as pre-catalyst does not play a major role, since equilibration in solution appears to lead to the same catalytically active species in most cases. $Ru_3(CO)_{12}$ is still to be considered an excellent catalyst precursor for ruthenium-catalyzed reactions because, unlike monomeric $Ru(CO)_5$, it is bench-stable in the air at room temperature. However, the initial idea that the catalytically active form is the intact cluster should be dismissed. Indeed, it has been clearly shown by kinetic and high-pressure IR studies that not only under catalytically relevant conditions the cluster is almost completely fragmented into mononuclear species, whether in the presence[26-27] or in the absence[28-29] of ligands, but also that any residual cluster would be less reactive than the monomer.[28]

Rhodium clusters are known to disproportionate in the presence of basic ligands or solvents[30] and the products of this disproportionation may be further reduced under the action of CO. Several species may be present under the reaction conditions and it is impossible to univocally attribute the observed reactivity to a single catalyst. However, it has been shown that the anionic $[PPN][Rh(CO)_4]$ (PPN^+= $(Ph_3P=N=PPh_3)^+$) mononuclear species is a more active catalyst precursor in the carbonylation of nitroarenes than any cluster[31-32] and some mechanistic studies support the view that this is the species responsible for the initial activation of the nitroarene.[17-18] The large organic PPN^+ cation is preferable to alkali metal cations because the latter more easily induce rhodium aggregation to give cluster species, although on a longer timescale PPN itself can led to a deactivation of the catalyst by the formation of a rhodium cluster having an interstitial phosphorus atom.[33-34]

As far as palladium catalysts are concerned, it is well established that when carbonylation reactions of nitroarenes to give carbamates are involved, the counteranion should be non-coordinating.[35-37] However, this conclusion does not extend to the synthesis of nitrogen heterocycles. Although only in a few studies were several palladium precursors tested, it appears that differences in the results are usually small. Only in one case, the synthesis of carbazoles by reductive cyclization of *o*-nitrobiphenyls, was the use of palladium acetate found to be essential to obtain high yield of the cyclized product.[38] A possible reason for this effect is discussed later.

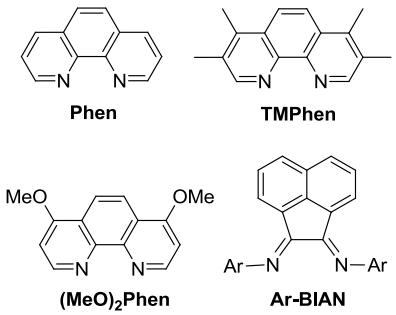
A separate class of catalysts based on molybdenum complexes is emerging since 2006, where the reductant is not CO, but is either a phosphine or a glycol. These will be described in a dedicated paragraph, since they are quite different from traditional ones.

2.4. Ligands

The most widespread ligands for transition metals are phosphines and these have also been used in the context of reduction/carbonylation reactions of nitroarenes, whether to give heterocyclic compounds or not. However, phosphines can react with nitroarenes even in the absence of any metal to give phosphinoxides and they have been employed as stoichiometric reductants for this purpose many times, as mentioned previously. Indeed, it has been shown already many years ago that phosphines are completely oxidized by nitroarenes under typical catalytic reaction conditions.[39] This may not be a major concern on the laboratory scale, where the catalyst and ligands are usually trashed at the end of the reaction and the products separated by column chromatography. However, oxidation of the ligand would not be acceptable on an industrial scale, both because of the cost of the phosphine and because separation of the products from phosphinoxides by crystallization has been shown to lead to unacceptable losses.[40-41]

Heterocyclic carbenes have also become popular in recent years, but no example of their use in the context of nitroarene reduction/carbonylation has been reported in the literature. We have attempted to use heterocyclic carbenes since their first reports as ligands in the early '90s and further made several attempts later employing both chelating alkyl-substituted and monodentate aryl-substituted imidazolium-based heterocyclic carbenes, but we never observed any significant reduction of the nitroarene under any of the experimental conditions attempted. Though we do not have an explanation for this failure, these ligands do not appear to be promising in the nitroarene field.

For the reasons given above, it is not surprising that the most widely employed ligands in this field are nitrogen ligands. Indeed nitrogen ligands are quite resistant to oxidation. As they are weaker than phosphines or carbenes, chelating ligands have almost exclusively been employed and among these the most useful ones are 1,10-phenanthroline and its derivatives for palladium and bis(arylimino)acenaphthene (Ar-BIAN) compounds for ruthenium (Scheme 1).



Scheme 1. Typical ligands employed in transition metal-catalyzed reductive cyclization reactions of nitroarenes by CO.

These ligands share the ability to stabilize both high and low oxidation state metal complexes and to act as non-innocent ligands.[42-45]

Concerning phenanthrolines, the introduction of donating groups usually improves performance. Among the most useful ligands, 3,4,7,8-tetramethyl-phenanthroline has been employed in nitroarene cyclization reactions for many years.[46] More recently, 4,7-dimethoxy-phenanthroline was found to give even better results.[23, 47] Phenanthrolines are easily displaced from palladium at high temperature and an excess of the ligands (typically from 2 fold to 16 fold) is always necessary to keep the catalytic system stable. Note that the lower the metal content is

(the highest the catalytic ratio), the higher the ligand excess must be. Indeed, the position of the ligand coordination equilibrium is affected by dilution. It is also worth of note that non-symmetric phenanthrolines, having inequivalent pyridinic rings, have been found to be better ligands than their corresponding symmetric analogues when the carbonylation reaction of nitrobenzene to methyl phenylcarbamate was investigated.[48-49] This appears to be due to the enhanced hemilability of the non-symmetric ligands, which is important in the carbonylation reaction.[50-51] However, no improvement was observed by using non-symmetric phenanthroline when they were employed as ligands in a reductive cyclization reaction,[47] indicating that hemilability is not important for these reactions.

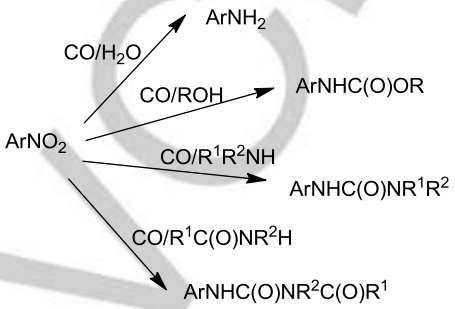
Bis-imines are typical ligands for transition metals, but they are weak compared to phenanthroline[52-54] and simple diimines are easily decomposed if employed under forcing conditions. The problem is remarkable when diimines are reacted with low valent ruthenium carbonyl compounds, such as those employed as catalysts for nitroarene reductive cyclization reactions, because easy breaking of the central C-C bond occurs.[55-56] With respect to most diimine ligands, BIAN derivatives are more rigid and this rigidity not only imposes the correct geometry for coordination, but also imparts a high chemical stability with respect to hydrolysis and rupture of the central C-C bond.[57-58] Ar-BIAN ligands have become quite popular in recent years for a number of reactions, but mostly in the field of palladium- and nickel-catalyzed polymerization of olefins.[59] To be efficient in the latter reaction, it is essential for the ortho positions of the aryl rings of the ligands to be substituted with bulky alkyl groups. On the contrary, sterically encumbered Ar-BIAN ligands are not efficient for nitroarene cyclization reactions.[26]

Söderberg and his group have reported in several papers (see later) the use of a palladium-based catalytic system comprising both a phosphine (usually 1,3-bis(diphenylphosphino)propane, DPPP) and phenanthroline and the combined ligands appears to give better results that the separate ones in at least some cases. No explanation has been given for this effect, but since phosphines are much stronger ligands than phenanthrolines, it is very likely that only the phosphine coordinates to palladium in the initial stages of the reaction, to give a very active catalyst. As the reaction proceeds, the phosphine, that is only present in a 1:1 mol ratio with respect to palladium, is unavoidably oxidized and the catalyst would deactivate in the absence of other ligands. We suggest that the presence of phenanthroline ensures that the catalyst remains active up to the end of the reaction, even if with a reduced activity with respect to the phosphine-coordinated one.

2.5. Solvents

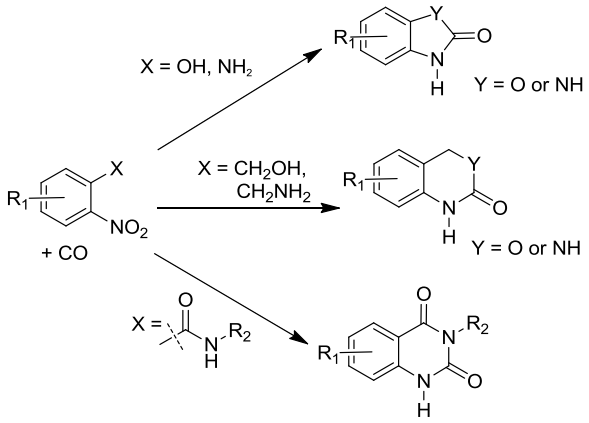
Concerning the use of CO as a reductant, it should be noted that the CO/H_2O couple act as a very selective reducing system for the nitro to amino group.[1, 6, 58, 60-61] This reduction is faster than any cyclization reaction and when water is present, formation of anilines invariably occurs. For this reason, anhydrous solvents should always be used to synthesize heterocycles.

Alcohols can also act as proton sources and generate aromatic amines, which react with the cogenerated alkoxycarbonyl complexes to finally yield carbamates.[18, 28-29, 51, 62-65] If no alcohol is present, but an equimolar or larger amount of an amine with respect to the nitroarene is present, ureas are formed, again through the intermediate formation of aromatic amines.[28, 66] Finally note that even amides can enter the same kind of reaction to yield acylureas (Scheme 2)



Scheme 2. Typical products formed in the presence of protic reagents.

Since carbamates can be thermally cracked to yield isocyanates, carbonylation reactions of nitroarenes in the presence of alcohols constitute a phosgene-free synthetic pathway to these important base chemicals. These reactions are outside the scope of this review and the interested reader should consult one of the available reviews.[1, 4, 7, 21, 67-68] With respect to the topic of this review, it is clear that any solvent containing –OH or –NH groups should be avoided. However, we must mention here that if the –OH or –NH group is already present in a suitable position in the starting nitroarene, it may be involved in an easy *intra*-molecular cyclization reaction (Scheme 3).



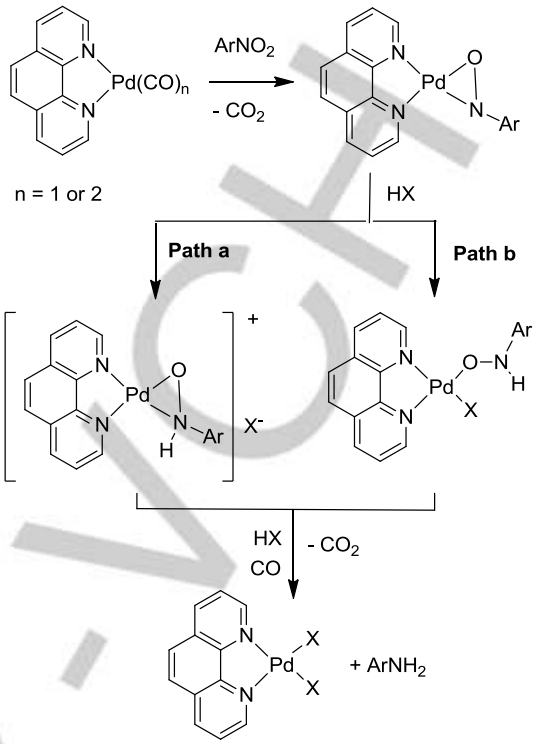
Scheme 3. Cyclization reactions involving a -OH or –NHR group already present in the molecule.

Since these reactions proceed by the intermediate reduction of the nitro group to amino, they will not be considered in detail here. The reader is addressed to the other cited reviews.

Coming back to the use of suitable solvents, the nature of the activation step of the nitroarene, which proceed by intermediates that are more polar than the starting material, results in the reactions being accelerated by polar solvents. Taking into account also selectivity problems and CO solubility, the solvents which most often give best results are medium to high polarity non-protic solvents such as THF, 1,2-dimethoxyethane, acetonitrile and dimethylformamide. The latter, in particular, has been found to allow for the mildest experimental conditions,[38, 40] although difficulties in removing it and toxicity issues may make another solvent preferable when reactivity differences are small.[69]

2.6. Additives

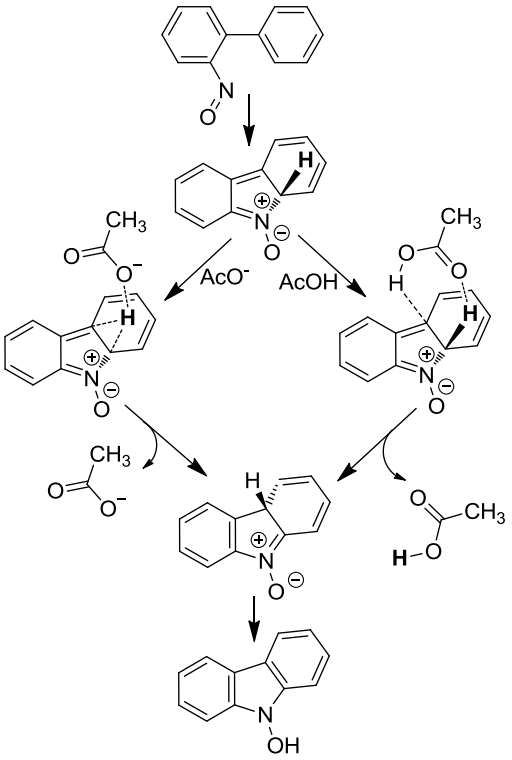
The addition of a weak base such as triethylamine to palladium/phenanthroline catalysts was found to be beneficial in several cases, though not always. The reason is not known for sure, but it may be contrasted with the positive effect that acids have on the carbonylation of nitroarenes to methyl arylcarbamates.[37, 64-66, 70-72] In the latter case, contrary to the reactions described in this review, the reaction proceed through the intermediate formation of anilines[51] and the role of the acidic promoter appears to play at least two different roles. One is to act as a bifunctional promoter, accelerating a proton transfer in the rate-determining carbonylation of aniline, and is well understood.[51] The other is the increase in the selectivity into carbonylated products by a corresponding decrease of the amounts of azo- and azoxyarenes formed. For this effect, an undisputable explanation has not yet been given, but use of mixtures of deuterated nitrobenzene and undeuterated aniline showed that azo- and azoxy-compounds contain exclusively the aryl moiety deriving from nitrobenzene, with no inclusion of that derived from aniline.[66] Thus, coupling of the two nitrogen-containing fragments occurs before aniline is generated. We have previously proposed that protonation of an intermediate nitrosoarene complex may be responsible for accelerating the formation of aniline (Scheme 4).[73]



Scheme 4. Possible role of acidic promoters in the reduction reactions of nitroarenes by CO. Adapted from.[73]

This is exactly what should be avoided to get high selectivities in reductive cyclization reactions and it can be proposed that the role of the base is to prevent any accidental protonation of the intermediates of the reaction.

We have mentioned in paragraph 2.3 that acetate was found to be an essential component of the palladium/phenanthroline catalytic system for the reductive cyclization by CO of *o*-nitrobiphenyls to carbazoles.[38] No explanation was given for this effect. However, the cyclization step has been calculated to require an isomerization step with a relatively high-energy barrier[74] and we propose that acetate or acetic acid (formed during the reduction of palladium) may help this step, the latter by acting as a, possibly bifunctional, catalyst (Scheme 5).



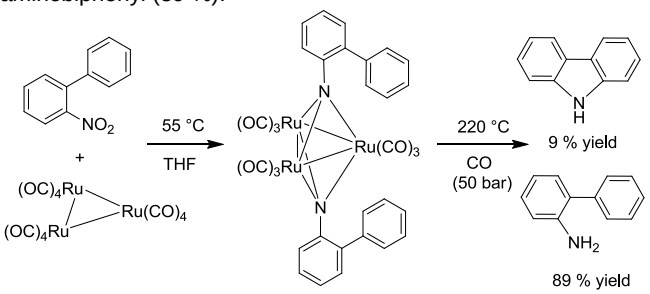
Scheme 5. Possible role of acetate and acetic acid in the cyclization of nitrosobiphenyl to *N*-hydroxycarbazole

When $Ru_3(CO)_{12}$ is employed in the absence of other ligands, the addition of halides, especially chloride, is beneficial.[75] The effect was first reported for carbonylation reaction of nitroarenes[76-77] and considered for many years to be an activation of an intermediately formed triruthenium imido cluster of the kind $Ru_3(CO)_{10}(\mu_3\text{-NAr})$.[78-79] However, it has now been conclusively shown that the only relevant role of chloride or other halides under the catalytic reaction conditions is to accelerate the equilibration of the catalytically inactive cluster into the active $Ru(CO)_5$ monomer, which would otherwise be slow with respect to the reaction time scale (see also above).[28]
The role of basic ligands and solvents in promoting the disproportionation of rhodium cluster has been mentioned in paragraph 2.3. Here we can mention that 2-hydroxypyridine has been found to be a promoter for the reductive cyclization of nitrostyrenes to indoles.[80] Importantly, the isomeric 4-hydroxypyridine and even simple pyridine inhibited the reaction rather than promoting it. Though at the time the effect was reported no explanation could be given for this effect, it may be due to a bifunctional effect analogous to the one discussed above for acetic acid. 2-Hydroxypyridine is indeed known to act as a bifunctional catalyst because of its equilibrium with 2-pyridone (Scheme 6).

Scheme 6. 2-Hydroxypyridine – 2-pyridone tautomeric equilibrium

2.7. Reaction intermediates

The intermediates formed during the reaction, both purely organic compounds and metal complexes, obviously vary depending on the specific reaction and catalyst considered. However, some general considerations are valid, that is worth mentioning here because they often emerge from an analysis of many different papers, rather than having been demonstrated in a single work.
The first point to be discussed is the identity of the species responsible for the cyclization step. With the exception of those reactions, not considered in this review, in which the intermediate is clearly an amine and a suitable leaving group or an aldehydic/keto group are present in the molecule, the reactions have been often proposed to proceed through an intermediate imido complex (often improperly named a nitrene complex). This proposal is the only one given in the older literature, but it is common even nowadays. However, it should be noted that there is little, if any, experimental evidence in its favor. Mononuclear imido complexes of late transition metals in a low oxidation state are extremely rare and reactive and no such complex has ever been isolated or characterized in solution that may be relevant to the cyclization reactions here discussed. Trinuclear ruthenium and iron clusters having a triply bridging arylimido group are on the other hand well known and relatively stable. The only experimental evidence for the involvement of an imido group in a nitroarene reductive cyclization is the series of reactions shown in Scheme 7. Here Cenini and coworkers showed that a ruthenium cluster containing two bridging imido groups derived from *o*-nitrobiphenyl afforded carbazole when heated at 220 °C under 50 bar CO, albeit in only 9 % yield, the main product being *o*-aminobiphenyl (89 %).[81]



Scheme 7. Carbazole production from an isolated bis-imido cluster

However, we have previously mentioned that following studies showed that trinuclear ruthenium cluster play no significant role in ruthenium-catalyzed reductive carbonylation reactions of nitroarenes[28-29] and it is very unlikely that this does not hold for

nitroarene cyclization reactions run with the same catalyst precursor and promoters. Thus, we can conclude that an active role of imido complexes in the reaction is unsupported by experiments, at least as the main reaction pathway.

On the other hand, nitrosoarenes are well-recognized intermediates in reduction reactions of nitroarenes by different means and evidence has accumulated during the years for an active role of these compounds, either free or coordinated, in this crucial step. The first direct evidence for this in transition metal catalyzed cyclization reactions was the observation that *N*-hydroxyindoles and *N*-hydroxyquinolones accumulate during the palladium/phenanthroline catalyzed cyclization reaction respectively of *o*-nitrostyrenes to indoles and *o*-nitrochalcones to quinolones.[82] Both products were present in larger amounts in the early stages of the reaction and converted to the final, deoxygenated, compound as the reaction proceeded. This indicates that they are not byproducts, but reaction intermediates. Although this was the first case in which these kind of products were detected after transition metal catalyzed reactions, it should be acknowledged that the formation of *N*-hydroxy derivatives had been observed much earlier after traditional Cadogan-Sundberg reactions using triethylphosphite and that nitrosoarenes had been proposed to be relevant aminating agents as early as 1965.[83] Note that the origin of the oxygen atom in the *N*-OH or *N*-OEt groups in the compounds isolated after a reductive cyclization by triethylphosphite was long ambiguous, because even the ethoxy groups on the phosphite may have originated them. However, it has been more recently demonstrated by isotopic ^{18}O labelling that the oxygen atom originates from the nitro group exclusively, in accord with the cyclization occurring at the nitrosoarene stage even for this classic reaction.[84] More papers have appeared since the first was published where the formation of *N*-hydroxy derivatives has been observed,[40, 85-88] which are inconsistent with the cyclization proceeding through an imido complex or a free nitrene. Finally, several theoretical studies have been published that show the plausibility of the cyclization of *o*-nitroso-styrenes and –biphenyls to give respectively indoles and carbazoles even outside the coordination sphere of a metal.[74, 89-90].

That the cyclization step occurs at the nitrosoarene stage at least in the case of the synthesis of indoles from *o*-nitrostyrenes is also indicated by the fact that nitrosoarenes react very quickly with alkenes even at low temperature. An *intra*-molecular cyclization reaction should proceed even more rapidly and indeed *o*-nitrosostyrene or related molecules not only cannot be isolated, but have never been even observed or trapped, despite several attempts to do so. A clear-cut example is the oxidation of an *ortho*-hydroxylamino-azastyrene derivative, that directly afforded the corresponding aza-*N*-hydroxyindole even at 0 °C, without allowing for the observation of the supposed nitroso intermediate.[91].

There is no doubt that nitrosoarenes are also involved in some *inter*-molecular cyclizations, where the reaction can also be conducted step by step and the direct reaction of the substrate with nitrosoarenes in the absence of other reagents can be observed and investigated directly. An active role of the metal in the cyclization step seems not to be required in some cases, but may be involved in others. These specific cases will be discussed in the relevant sections of this review.

Finally, the doubt may arise that arylamines are involved at the cyclization step even in some reactions were no leaving group is present. For example, it is well known that *o*-aminostyrene and its analogues can cyclize to indoles in a palladium-catalyzed reaction if an external oxidant is present[92] and a nitroarene may play this role in the way to its reduction to arylamine. We have dealt with this problem several years ago by running a series of competitive reactions between differently substituted nitro- and amino-derivatives that could give the same kind of cyclized product, but with different substitutional patterns, so that the substrate originating them could be identified.[93] We have discussed these results in detail in a previous review[3] and we will not do the same here. However, the conclusion is that arylamines are never intermediates in the main reaction pathway, but appear to be involved in a secondary pathway in some cases. The only exception are those reactions in which condensation with an aldehydic/keto group or formation of an amide from a pendant ester group can occur. In these cases, the condensation was shown to proceed through the intermediate formation of an amine even when the reaction had been proposed to involve an imido complex.[94]

2.8. Reactivity trends

Each of the reactions described in the following has its own peculiarities, as also have the different metals employed as catalysts. However, some trends are common and are worth to be discussed in general. Note that the principles mentioned below are sometimes useful to understand the differences in activity and selectivity reported in many papers even when no justification was given by the authors themselves for the obtained results.

Not all the trends are immediately visible from the data reported in individual papers because some effects may be only observable if reactions conditions are chosen, intentionally or not, in such a way to make a particular effect relevant. For example, variations in the rate of reaction of different nitroarenes will only be observable if the reaction conditions are chosen in such a way (*i.e.* short reaction times, low catalyst loadings) that the conversion of the starting material is not complete and if the amount of unreacted substrate is measured. This is rarely done, since most studies are aimed at maximizing the isolated yield of the product. So reaction conditions are chosen that afford complete conversion of the substrate in most cases and no data is reported that allows distinguishing if a low yield was due to a low conversion of the reagent or to a low selectivity in the desired product. Analogously, factors affecting catalyst stability may only be observed when attempts are made to lower the catalyst amount to less than 1 mol-%, since large amounts of catalyst may result in complete substrate conversion even if the catalyst is extensively deactivated during the reaction. Thus, only by comparing many data from different reports, the trends emerge in their clarity.

The first trend is on the influence of the substitution pattern on the nitroarene on the reaction rate. Few of the reactions

described in this review have been the object of a detailed kinetic analysis, but in all the cases in which the latter was performed, the kinetics was found to be first order in nitroarene.[26, 95-96][97] The only exception is a reaction in which a silane, not CO, is the reductant.[88] Here, the reduction of the metal catalyst at the end of the catalytic cycle is the rate-determining step of the reaction. That nitroarene activation is the slowest step of the reaction is likely to be the rule even for other reactions/catalysts, as also indirectly shown by synthetic results. Indeed, the possible intermediates in the reaction, nitrosoarenes or imido complexes, are all much more reactive than nitroarenes and the only steps of the reaction that are likely to be rate-determining are the initial activation of the nitroarene or the regeneration of the catalytically active metal species at the end of the cycle. Since the active species appears to be regenerated automatically with the last step of the catalytic cycle in most cases, it is not surprising that the nitroarene activation is the slow step very frequently, if not always.

We have mentioned earlier that the activation of nitroarenes starts with an electron transfer from the metal to the nitroarene. Accordingly, more easily reduced nitroarenes react at a faster rate. A linear correlation between the electrochemical reduction potential of a series of *o*-nitrostyrenes and the logarithm of their rate of cyclization with a Pd/Phen catalyst has been found.[40]

Two factors affect the reduction potential of nitroarenes. The first is obviously the electronic influence of the substituents present, with electronwithdrawing substituents affording faster reactions than electrondonating ones. The second is the steric influence of substituents in the *ortho* position with respect to the nitro group. It has long been known that *o*-nitrotoluene has a more negative reduction potential than *p*-nitrotoluene, despite electronic effects should be roughly the same.[98] The effect is due to the fact that the presence of an *ortho* substituent causes a tilting of the plane of the nitro group with respect of that of the phenyl ring and this decreases the efficiency of the delocalization of the negative charge in the reduced species. Such an effect is clearly present for all *intra*-molecular cyclization reactions, but can justify some smaller differences between apparently similar substrates. For example, it has been found that *E*-(2-nitro)stilbene reacts at a faster rate than its Z isomer.[85, 99] This can be correlated with the larger steric congestion in the latter molecule, in accord with the more negative reduction potential of *E*-(2-nitro)stilbene with respect to *Z*-(2-nitro)stilbene.[99]

The nature of the nitroarene activation step is also responsible for the better results often obtained with more donating ligands. This effect has been discussed above in paragraph 2.4.

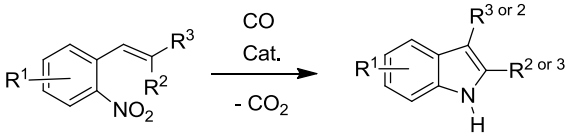
Nitrosoarenes are electrophilic and the coupling partner usually act as a nucleophile. Thus, on one hand the same electronwithdrawing groups on the nitroarene that accelerate its initial activation also makes the cyclization more effective. On the other, more electron-rich coupling partners in the cyclization step should give faster reactions and, conversely, very electron-poor ones may react sluggishly or not at all. These trends are usually observable clearly only for *inter*-molecular reactions. However, they are often difficult to observe for *intra*-molecular reactions. Indeed, an electrondonating group on the coupling moiety will decrease the reactivity of the nitroso group by an inductive effect, so that an internal compensating effect arises between the two coupling partners. Moreover, an effect on catalyst stability may be present, which obscures the reactivity trend if not separately quantified. Such an effect has been noted for the palladium/phenanthroline catalyzed synthesis of indoles from *o*-nitrostyrenes when the reaction was conducted in a flow apparatus.[85] Because of the reactor set-up, to be discussed later, decomposition of the catalytic system to give metallic palladium was observed when the reagents and CO were mixed at room temperature, before entering the heated loop. It was noted that when the styrene was substituted with an electronwithdrawing group the catalyst was still active in a second run, whereas it was completely or almost completely deactivated in its absence. Methyl *o*-nitrocinnamate was especially effective as stabilizer. On the other hand, coordination of alkenes lacking electronwithdrawing groups to ruthenium,[26] iron[95] and palladium[100] complexes has been shown to activate the catalyst in some cases. This effect will be discussed later.

In at least two cases, both concerning the palladium-catalyzed *intra*-molecular cyclization of an *o*-nitrostyrene to indole, it has been reported that the addition to the reaction mixture of a nitroarene lacking any substituent that can lead to a cyclization process inhibits the reaction. Thus, not only the simple nitroarene is not significantly converted into any product, but its presence strongly decreases or even completely blocks the reactivity of the nitrostyrene.[85, 101] Although no explanation has been given in either of these two papers for the observed deactivation, it should be recalled that the reaction between palladium/phenanthroline complexes and nitroarenes under CO pressure and in the absence of protic solvents leads to the formation of several metallacyclic complexes.[102-106] These need the presence of an acid to be transformed into further products and indeed carbonylation of nitrobenzene to phenyl isocyanate by palladium/phenanthroline complexes requires the presence of an acid to proceed.[107] Under the conditions in which the cyclization reactions are performed, these metallacycles should be relatively stable and constitute a dead end of the catalytic cycle. A suitable functional group in the ortho position, or an external reagent for inter-molecular reactions, can intercept an intermediate in the reduction of the nitroarene before the metallacycle is formed.

3. Synthesis of *N*-heterocycles by *intra*-molecular cyclization reactions of nitroarenes employing gaseous CO as the reductant

3.1. Synthesis of indoles

Indoles are the class of heterocycles whose synthesis by reductive cyclization of nitroarenes has been most intensely investigated. The reaction was first reported by Cenini and coworkers in 1986, employing $Fe(CO)_5$, $Ru_3(CO)_{12}$, or $Rh_6(CO)_{16}$ as catalyst under forcing conditions (220 °C, 80 bar CO, Scheme 8).[108]



Scheme 8. General synthesis of indoles from *o*-nitrostyrenes.

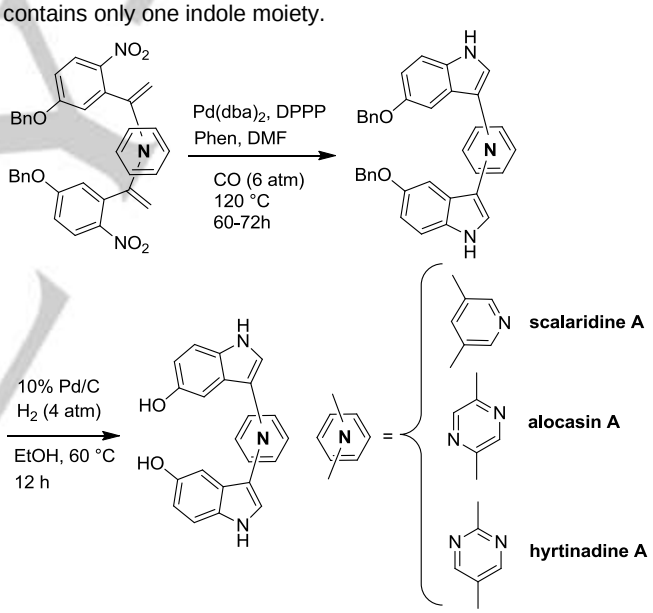
One result of this study that is still worth being mentioned is that if either R^2 or R^3 is hydrogen, this will always be found in the position 3 of the final indole, independent of the initial geometry around the olefinic double bond. If neither of the two is hydrogen, one of the two groups will migrate, with a phenyl group migrating in preference to a methyl one. This is the same preference that had been earlier found when the same cyclization had been conducted employing triethylphosphite as reductant[109] and is probably a general trend. Note that methyl migration was observed from a dimethyl derivative ($R^2 = R^3$ = Me in Scheme 8) even for a palladium catalyst,[110] but not when a rhodium catalyst was employed, where a mixture of products was obtained instead.[111]

On the other hand, the geometry around the double bond, *cis* or *trans*, in the case of disubstituted alkenes does not sensibly affect the reaction, a feature again in common with the triethylphosphite-promoted reaction.[109] Minor differences in the rate of reaction and in the yield of indole have been found when *cis* or *trans* 2-nitrostilbene were separately reductively cyclized, as also mentioned in the previous paragraph.[85, 99]

The group of Cenini also first reported the use of palladium catalysts with phenanthroline ligands, including TMPhen, for the same reaction, which allowed for the use of milder reaction conditions.[46] The palladium/phenanthroline catalytic system has been later optimized by Davies and coworkers using a multireactor system.[40] The best experimental conditions identified in this study (0.1 mol-% $Pd(O_2CCF_3)_2$, 0.7-1 mol-% TMPhen, 80 °C. P_{CO} = 15 psig, corresponding to ~ 2 bar absolute pressure or ~ 1 bar overpressure with respect to atmospheric pressure, in DMF) allowed almost quantitative yields in many cases at a very low catalyst loading, although 16 h are required to take the reaction to completion. Substitution of $Pd(O_2CCF_3)_2$, with $Pd(OAc)_2$ or of TMPhen with unsubstituted Phen decreased somewhat the yield, but not to a large extent so that the use of these much cheaper catalyst precursor and ligands should be considered for large scale applications. These experimental conditions are still the most efficient reported to date for the synthesis of indoles by reductive carbonylation of *o*-nitrostyrenes by gaseous CO. More recently, the same group extended the use of similar reaction conditions to the synthesis of indoles containing an amido group in the position 4 of the final product. The most interesting aspect of the reaction is that the final product could be obtained in a high isolated yield and purity without any need for a chromatographic purification by simply adding 1M H_3PO_4 to the reaction mixture at the end of the reaction. The phenanthroline used as ligand remained in the DMF/H_2O solution and the indole precipitated out of it with only minor losses.[41]

In the time frame covered in more detail in this review (2006-2018), most of the work in this area has been done by Söderberg and coworkers. The catalytic systems employed in the single cases are always one or more of the previously described combinations of a palladium precursor ($Pd(OAc)_2$ or $Pd(dba)_2$) and either a phosphine (PPh_3 or 1,3-bis(diphenylphosphino)propane, DPPP), a phenanthroline (Phen or TMPhen), or a mixture of the two. Although in some cases more than one system was employed, in others only one type of catalytic system was tested and the reported results do not allow to draw a general conclusion on which is more effective in each case. We recall from the discussion in paragraph 2.4, that the identity of the best system may even depend on the catalytic ratio or by the tendency of the substrate to react with the phosphine. Thus, in the following we will mostly focus on the synthetic achievements rather than on the specific catalytic system employed.

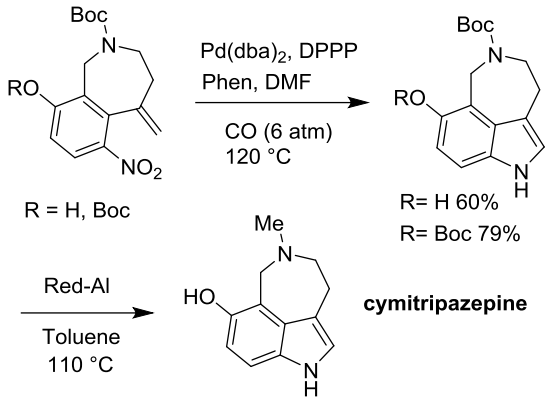
Several papers were devoted to the synthesis of indole alkaloids. A double cyclization of the kind here considered was employed as one of the steps in the synthesis of alkaloids scalaridine A, alocasin A, and hyrtinadine A (Scheme 9).[112] The same conditions were employed to synthesize hyrtinadine B, which contains only one indole moiety.



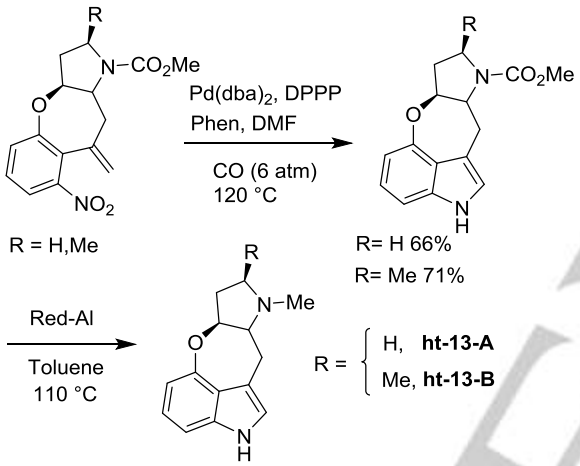
Scheme 9. Synthesis of some alkaloids containing two indole moieties.

The presence of the donating BnO- group may be responsible for the long reaction times required to take the reaction to completion.

The same catalytic system was employed to synthesize the tricyclic indole alkaloid cymitripazepine (Scheme 10),[113] from which fargesine was also obtained by oxidation, and the tetracyclic indole alkaloids ht-13-A and ht-13-B (Scheme 11).[114-115]

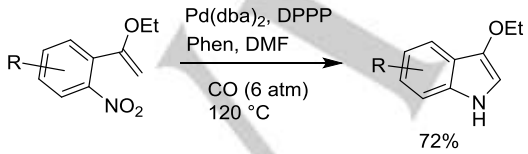


Scheme 10. Synthesis of a tricyclic alkaloid. Red-Al = sodium *bis*(2-methoxyethoxy)aluminum dihydride.



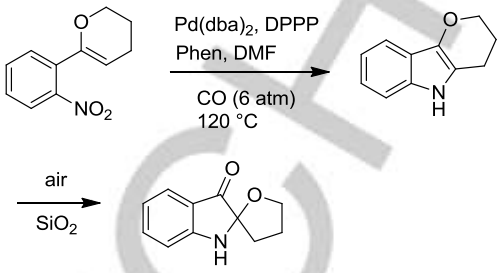
Scheme 11. Synthesis of two tetracyclic alkaloids. Red-Al = sodium *bis*(2-methoxyethoxy)aluminum dihydride.

Söderberg also investigated the effect of the presence of electrondonating or electronwithdrawing groups directly attached to the vinyl group. The effect of the presence of the formers was analyzed by investigating the cyclization reaction of a series of 1-(2-nitrophenyl)-1-alkoxy (mostly ethoxy) alkenes (Scheme 12).[116]



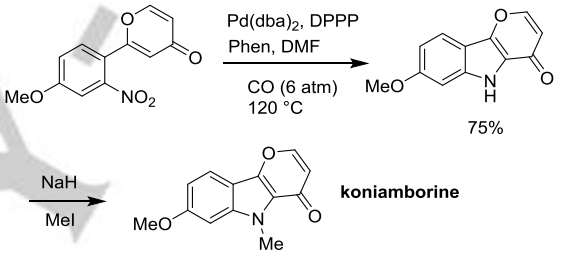
Scheme 12. Synthesis of 3-ethoxy-indoles

The reaction was successful both when the aryl ring bore electrondonating or electronwithdrawing and even when it was a pyridine ring, but both the starting alkenes and the products indoles were found to be unstable and slowly decomposed upon standing. The pyranoindole was found to be especially air sensitive and was completely or almost completely oxidized to a spiroindolone during the workup (Scheme 13).[116]



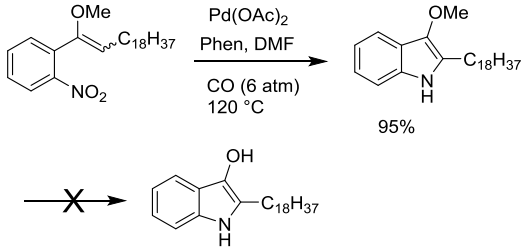
Scheme 13. Synthesis and oxidation of pyranoindole.

Given the success of the synthesis of 3-alkoxyindoles, the strategy was extended to the synthesis of the naturally occurring pyrano[3,2-*b*]indole koniamborine (Scheme 14).[117]



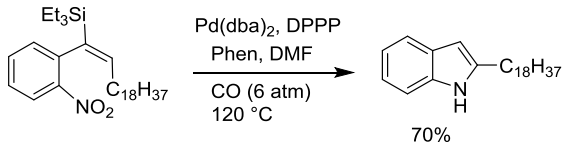
Scheme 14. Synthesis of koniamborine.

The synthesis of 2-octadecyl,3-methoxyindole by the same catalytic system unexpectedly failed, but use of the $Pd(OAc)_2$/Phen combination allowed the reaction to go to completion.[118] Attempts to transform the methoxy group into the hydroxy one, failed (Scheme 15).[118]



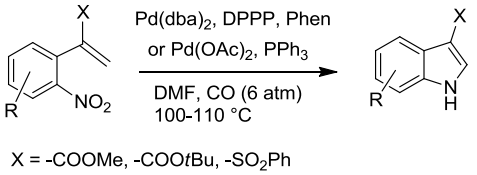
Scheme 15. Synthesis of 2-octadecyl,3-methoxyindole.

In the same work, the cyclization of a nitrostyrene bearing a triethylsilyl group in the α position was attempted. The indole was obtained in good yields, but the silyl group was lost in the process (Scheme 16).[118] Such a loss of a functional group is unprecedented in this chemistry, but there is no other data in the literature to confirm if it constitutes a general reactivity.



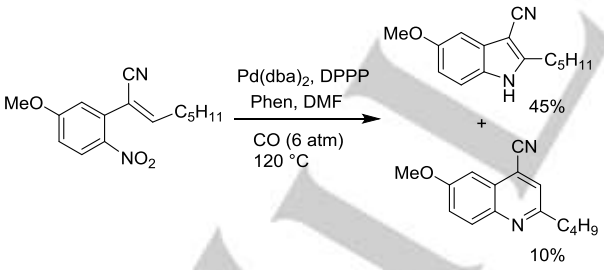
Scheme 16. Loss of the $–SiEt_3$ moiety during a cyclization reaction.

The effect of electronwithdrawing groups on the vinyl group was investigated by first examining the reactivity of a series of compounds having the –COOMe, -COO*t*Bu, or $–SO_2Ph$ in the α position (Scheme 17).[119]



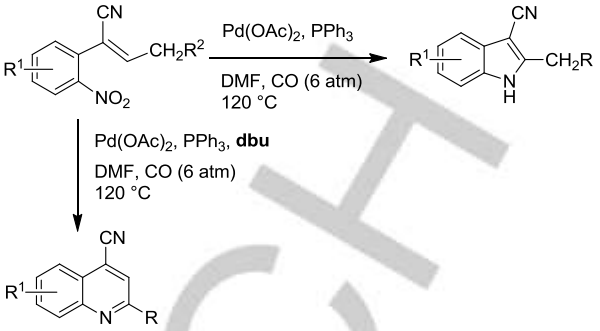
Scheme 17. Synthesis of indoles having electronwithdrawing groups in the 3 position.

The reaction was slower than with other nitrostyrenes, taking three days to be complete, which appears to be an effect of the stabilization of the catalytically active complex by coordination to the electronpoor alkene. Indeed, when the aryl ring was a pyridine ring having the nitrogen *ortho* to the vinyl group, the reaction was further slowed down, presumably because of the chelation of the pyridine and vinyl group, whereas no effect was noted when the pyridinic nitrogen was in the *para* position.
When the electronwithdrawing group was a cyano group and a pentyl group was present on the vinyl group, the synthesis of the indole was accompanied by the formation of a minor amount of quinoline (Scheme 18).[119]



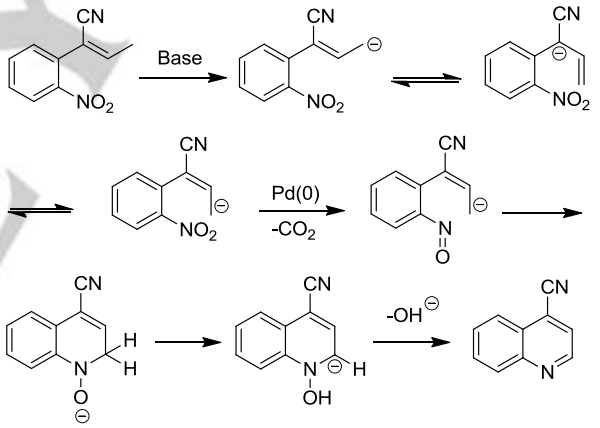
Scheme 18. Cyclization of an α- cyano nitrostyrene.

The selectivity of this intriguing reaction was examined in more detailed in a dedicated paper.[87] Among different variations of the catalytic systems tested, it was found that the use of the $Pd(OAc)_2/PPh_3$ combination in the absence of bases selectively gave the indole, whereas the addition of dbu to the same system resulted in the exclusive formation of the quinoline (Scheme 19).



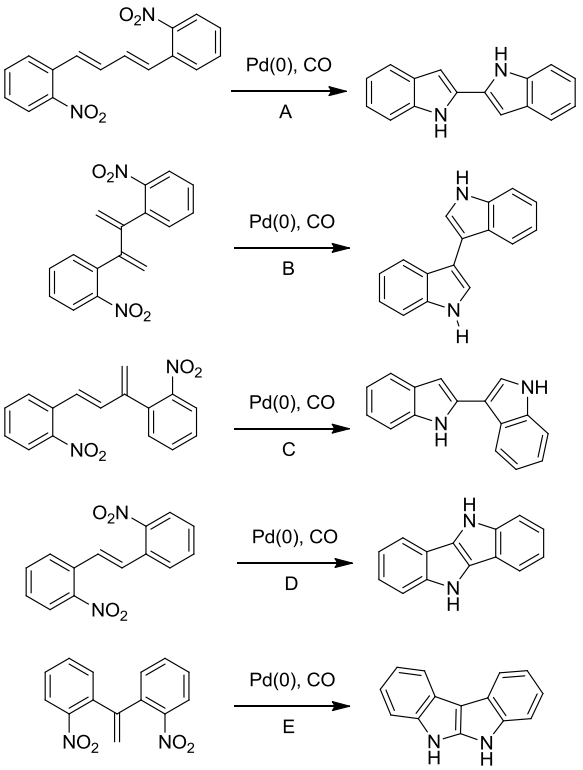
Scheme 19. Selective formation of either cyanoindoles or cyanoquinolines from cyano nitrostyrenes.

If the cyano group was replaced by an ester or phenyl group, only the indole was formed even in the presence of dbu, but use of the stronger base *t*-BuOK allowed competitively obtaining the quinoline in some cases.
The color change observed when the substrate and dbu are mixed clearly indicates that dbu is basic enough to deprotonate a C-H in the allylic position. From the available data, the most likely pathway for the formation of quinoline appears to be that shown in scheme 20.



Scheme 20. Proposed mechanism for the formation of cyanoquinolines.

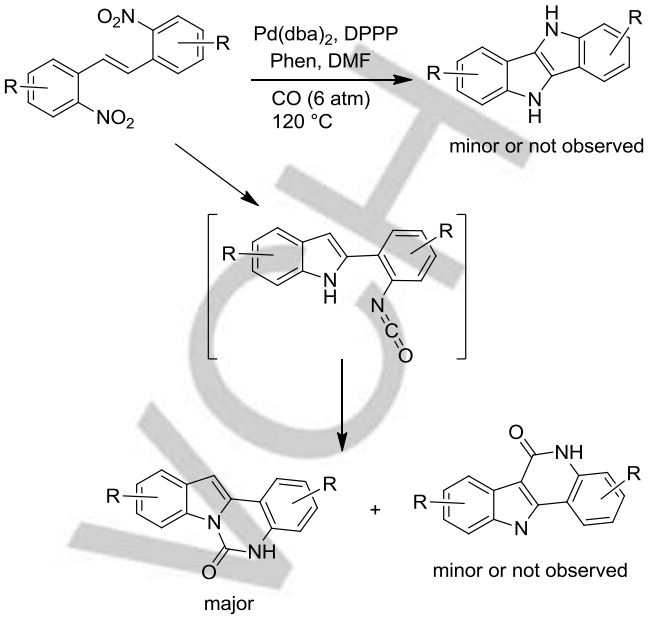
The synthesis of bis-indoles by a double cyclization reaction has been investigated extensively.[120] All possible coupling geometries for two indole nuclei were examined (Scheme 21).



Scheme 21. Coupling modes of two indole moieties.

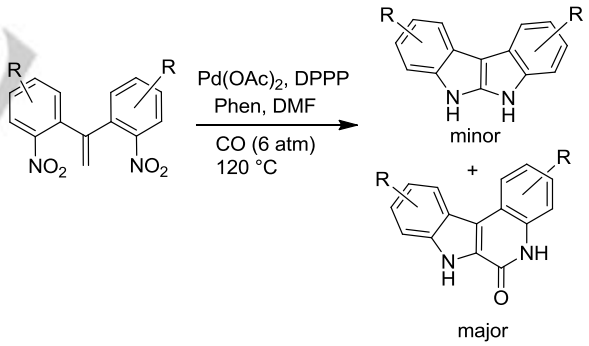
The same catalytic system previously employed for other related reactions was used ($Pd(dba)_2$/DPPP/Phen, 6 atm CO, 120 °C, in DMF). Cyclization modes A, B, and C in scheme 21 were successful for all tested substrates and gave high yields of the bis-indoles. However, the synthesis of fused bis-indoles (cyclization modes D and E) were much less effective and carbonylated products prevailed among the products.

Specifically, when several *o,o'*-dinitrostilbenes were subjected to type D reduction, the desired bis-indole was observed in only one case and in a 13 % yield (Scheme 22). The main product is a urea-type compound. This and a second byproduct may derive from an intermediately formed isocyanate. Carbonylation of simple nitroarenes by a palladium/phenanthroline system is known to give isocyanates catalytically[107] and these are also formed as intermediates under conditions where the finally observed product is a diarylurea or a carbamate.[51, 66]



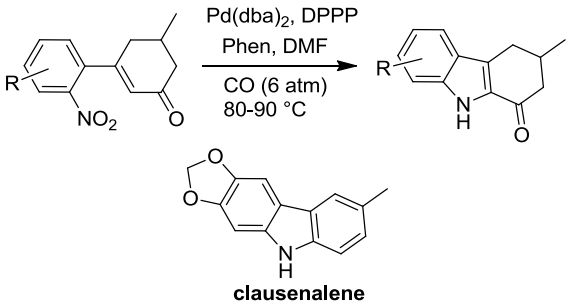
Scheme 22. Products obtained by cyclization of *o,o'*-dinitrostilbenes (reaction D in scheme 21).

The outcome was a bit better in the case of the geminally substituted olefin (type E reaction. Scheme 23). In this case, the yield of the bis-indole reached 30% in one case, but most of the reagent was always converted into a carbonylated derivative.



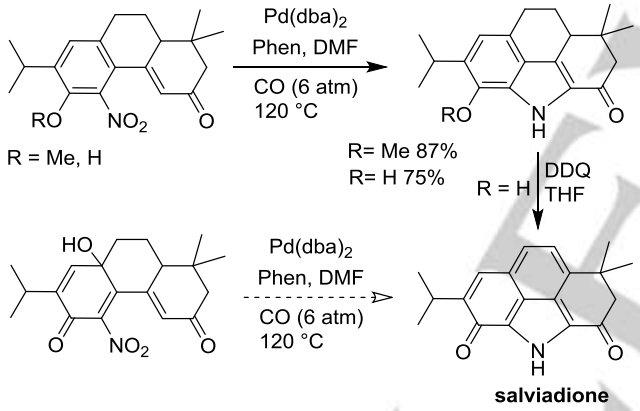
Scheme 23. Products obtained by cyclization of 1,1-*bis*(2-nitroaryl)ethylenes (reaction E in scheme 21).

The palladium-catalyzed reductive cyclization of nitrostyrenes was also employed to synthesize several tetrahydrocarbazolones, which can be employed as advanced intermediates in the synthesis of carbazole alkaloids such as clausenalene (Scheme 24).[121]



Scheme 24. Synthesis of tetrahydrocarbazolones.

The cyclization of an *o*-nitrostyrene was also employed as a step in the synthesis of salviadione (Scheme 25).[122] Attempted cyclization of the quinole (lower reaction in the scheme) resulted in the complete consumption of the reagent, but only gave small amounts of the desired dione, accompanied by a complex mixture of compounds. On the other hand, reaction of the corresponding phenol or anisole successfully gave an indole from which the dione could be obtained in good yields by oxidation with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), when the phenol derivative was employed.



Scheme 25. Synthesis of salviadione.

It should be noted that from the point of view of the heterocycles formed in the cyclization reaction, a successful cyclization of the quinole might have been considered as the first example of a metal-catalyzed reductive cyclization of a nitrodiene by CO, a reaction unprecedented at the time and that requires a more donating phenanthroline, $(MeO)_2$Phen, to be efficiently performed (see later).[23]

In the time frame covered in more detail in this review, Söderberg has also published a "Discussion Addendum"[123] to a previously published paper on the synthesis of indoles by palladium catalyzed reductive cyclization of *o*-nitrostyrenes.[124]

The cyclization of several nitrostyrenes was also investigated in a flow apparatus.[85] Some of the results of this study have already been mentioned in paragraph 2 and will not be discussed again here. The apparatus consisted of an HPLC pump which introduces the mixture of nitrostyrene, catalyst ($Pd(OAc)_2$) ligand (best phenanthroline) and, possibly, tributylamine (the addition of which improved the results) to a mixer where CO, from a tank, was added before entering the reaction loop. A cooling loop and a back-pressure regulator completed the system. Among the tested solvents, acetonitrile and DMF gave higher conversions and selectivities, whereas dioxane and ethyl acetate led to lower conversions and to the formation of relatively large amounts of what appeared to be *N*-hydroxyindoles. The reaction was successful for several nitrostyrenes and only failed with *o*-nitrocinnamic acid. In this case, products attributable to the reduction of the nitro group to amino and, in one case, decarboxylation of the acid were obtained. This is in line with what earlier said on the need to avoid proton sources when cyclization reactions of nitroarenes are performed

The mixer was a simple T-shaped Teflon tube at RT in early experiments, but was replaced by a heated mixer during the optimization of the reaction. Indeed, it was observed that metallic palladium is immediately deposited in the Teflon tube when CO and the catalyst are mixed at room temperature. This is because the reduction of palladium acetate by CO is rapid even at RT, whereas the reaction of the so formed Pd(0) complex with nitroarenes only occurs at higher temperatures. Palladium carbonyl complexes with nitrogen ligands are not stable and easily decompose to metallic palladium. When standard reactors are employed, it is common to observe metallic palladium formation after the nitroarene has been completely consumed. However, no metallic palladium is formed before that if the correct experimental conditions are employed. Mixing CO and the reagents in a heated mixer improved the results, but extensive palladium plating was still observed, which needed a washing with aqua regia to be removed. Thus, the fast mixing of liquids and gases that constitutes the main advantage of flow techniques constitutes also a limit when applied to the present reaction. The system anyway allowed the reaction to be completed in a short time (around 15 min), although at a temperature (140 °C) relatively high with respect to that employed by Davies[40] (80 °C) and with a tenfold larger amount of catalyst.

The reaction was scaled up to 12 mmol of methyl 2-nitrocinnamate and the product spontaneously crystallized out of the crude reaction mixture in 84 % yield. ICPMS analysis showed that it contained 45 ppm of palladium, which could be reduced to 16 ppm by crystallization.

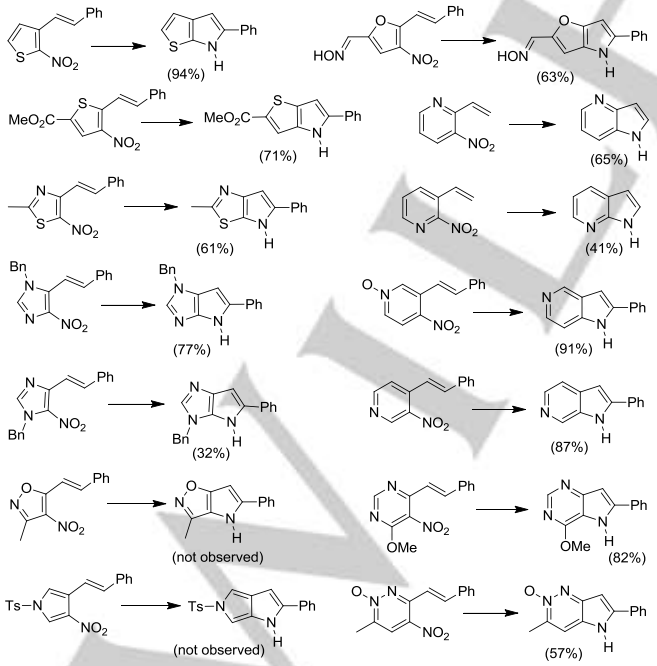
It appears that the use of flow reactors has a strong potentiality in the field of the reductive cyclization reactions by CO here described, but a way of dosing the CO addition in such a way that metallic palladium formation does not occur must be found.

In recent years, only one report has been published on the use of a transition metal different from palladium for the reductive cyclization of nitrostyrenes by CO. The ionic rhodium complex $[Rh(CO)_2(Me_2NCH_2CH_2NMe_2)][Rh(CO)_2Cl_2]$ was employed as catalyst under mild conditions (100 °C, 100 psi, ~6.8 bar, in THF).[111] The use of a different rhodium precursor, $[Rh(COD)Cl]_2$, either alone or in the presence of different phosphines, was ineffective. The reaction worked well even

when the substrate contained an aldehydic or keto group bound to the alkene, with no quinoline being formed. It is not obvious which is the active species in this system. No reaction between a rhodium(I) complex and a nitroarene has ever been reported and rhodium(I) compounds may be reduced under the reaction conditions. We have previously mentioned that there is some evidence that $[Rh(CO)_4]^-$ may be involved in these reactions and such compound catalyze indeed the same indole synthesis.[80] Unfortunately, reaction conditions are too different to allow a comparison between the catalytic activity of the two systems.

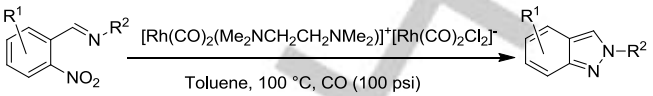
3.2. Synthesis of other 5-membered *N*-heterocycles

The reactivity described in the previous paragraph was extended by Söderberg to a series of substrates in which the aryl ring bearing the nitro group is replaced by a 5- or 6-memberded heterocycle.[125] With the exception of some pyridine derivatives, the other cyclization reactions were unprecedented, at least as far as the use of CO as the reductant is concerned. The starting nitro compounds were treated with CO (6 atm) and either a $Pd(OAc)_2/PPh_3$ catalytic system in CH_3CN at 80-90 °C or the $Pd(dba)_2$/Phen combination in DMF at 120 °C. The latter system gave in most cases higher yields of the cyclized product, although longer reaction times were required. This is in line with our suggestion that phosphines should afford catalysts that are initially more active, but deactivate with time. Scheme 26 shows the performed reactions and the best yield obtained. The only substrates for which no cyclized product was obtained are those in which the starting heterocycle was an oxazole or pyrrole ring. These are also the most electron rich ring systems among those tested and is not surprising that activation of the nitro group is difficult.



Scheme 26. Synthesis of bicyclic pyrrolo-fused heteroaromatic compounds.

The same ionic rhodium system cited in the previous paragraph also succeeded in catalyzing the reductive cyclization of *N*-(2-nitroarylidene)amines to 2*H*-indazoles (Scheme 27).[126]

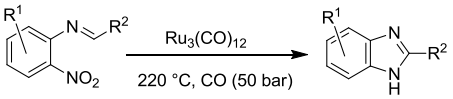


Scheme 27. Synthesis of 2*H*-indazoles.

Both electronwithdrawing and electrondonating substituents on the aryl ring were well tolerated, but R^2 need to be an alkyl group for the reaction to proceed with good yields. If R^2 was phenyl or allyl, 25% yield or trace amounts of the indazole were obtained. Moreover, only imines derived from an aldehyde were converted. No reaction was observed when the imine derived from *o*-nitroacetophenone and *n*-butylamine was employed as reagent.

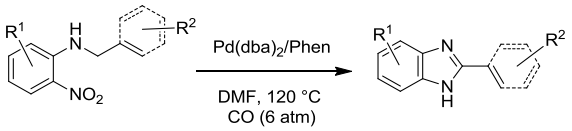
This reaction is noteworthy. Cyclizations of the kind shown in scheme 27 fail or give at best small amounts of indazole with most catalytic systems.[99, 127-128] In the previous literature, only one catalytic system, $Pd(PPh_3)_2Cl_2/SnCl_2$, successfully performed it.[110, 129] $SnCl_2$ has been typically employed in the older literature to activate noble metal chlorides because it can abstract the chloride from the coordination sphere of the metal and convert it to the $SnCl_3^-$ anion. The latter is isolobal to a phosphine and acts as a ligand. However, in the present case it should be noted that $SnCl_2$ reduces nitroarenes under much milder conditions than those employed for the catalytic reaction[130-132] and that an over-stoichiometric amount of $SnCl_2$ has even been employed to promote the reductive cyclization of *N*-(2-nitroarylidene)amines to 2*H*-indazoles in the absence of any metal catalyst.[133] Since the amount of $SnCl_2$ is not negligible (0.5 equiv with respect to the nitroarene) in the cited system, its role as a direct reductant cannot be dismissed. Reactions involving reduction of nitroarenes with stoichiometric $SnCl_2$ all proceed through the formation of *N*-hydroxylamines. Given the easy synthesis of indazoles when $SnCl_2$ is present and the failure to get these products when systems which are unlikely to produce hydroxylamines are employed, it is tempting to suggest that formation of the latter is an essential requisite to get indazoles and that the rhodium catalyst mentioned above is one of the few systems efficient in affording such intermediates. However, this is admittedly speculative at the moment.

The reverse orientation of C=N double bond in the starting material has long been known to yield benzimidazoles when the reaction is catalyzed by $Ru_3(CO)_{12}$ (Scheme 28).[127]



Scheme 28. Synthesis of benzimindazoles from *N*-(2-nitrophenyl)imines.

More recently, Söderberg attempted to effect the same cyclization reaction employing either $Pd(OAc)_2/PPh_3$ or $Pd(dba)_2$/DPPP/Phen as the catalytic systems.[86] The reaction failed in both cases when R^2 was a phenyl group, but the benzimidazole could be obtained in a low to good yield in two cases, when employing an imine derived from an aliphatic ketone or aldehyde. Note that the imine had to be prepared by an aza-Wittig reaction employing an arylazide, an aldehyde and PPh_3 as reagents. Reaction of nitroanilines with aldehydes did not afforded the expected imines, but isomerized vinylimines. Since the main products when the latter compounds are reductively cyclized are usually six-membered nitrogen heterocycles, this work is better described in the next paragraph.
On the other hand, the same group succeeded in preparing benzimidazoles by a reaction involving a methylene group in the *alpha* position with respect to the amino group. The only requisite is that the methylene group should be activated by being in an allylic or benzylic position (Scheme 29).[134]

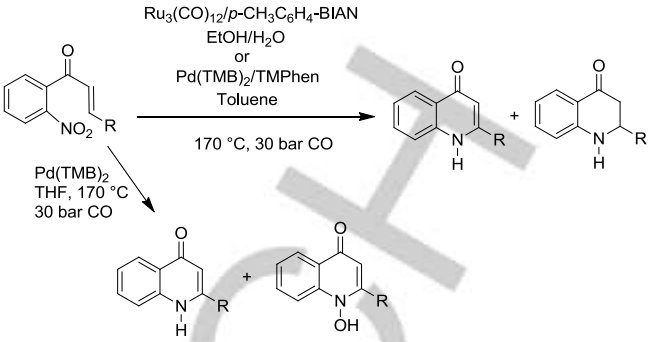


Scheme 29. Synthesis of benzimindazoles by activation of a methylene group.

Best results were obtained by working in DMF with only phenanthroline as ligand for palladium and 6 atm CO. Electronwithdrawing and electrondonating substituents are tolerated both on the aryl ring containing the nitro group and, when present, on the benzylic ring.
The reaction is noteworthy, being one of the very few examples of nitroarene cyclization reactions of the type discussed in this review to proceed by an activation of a sp^3 C-H bond.

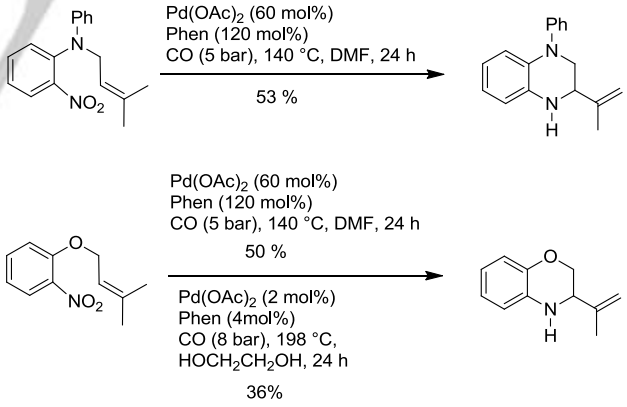
3.3. Synthesis of 6-membered *N*-heterocycles

The synthesis of 6-membered *N*-heterocycles by nitroarene reduction has traditionally been more problematic than that of 5-membered ones, affording only small amounts of products, except for the synthesis of benzoquinolones from nitrochalcones (Scheme 30).[82, 135-136]



Scheme 30. Synthesis of benzoquinolones and related products. TMB = 2,4,6-trimethylbenzoate.

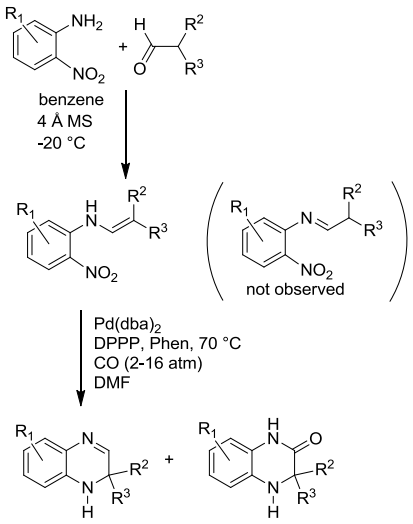
The reaction can be catalyzed by either $Ru_3(CO)_{12}$/*p*-$CH_3C_6H_4$-BIAN or $Pd(OAc)_2$/TMPhen and is accompanied by the formation of a variable amount of the saturated quinolinone, whose amount is higher when the ruthenium catalyst is employed. If the TMPhen ligand was omitted and dry THF was employed as solvent, the corresponding *N*-hydroxy quinolone was also obtained. The observation of this intermediate further supports the conclusion drawn by a previous mechanistic study that the quinolinone derives from a Michael addition of an intermediately formed amine onto the vinylketone moiety, but the formation of the quinolone does not involve amine formation.[93]
More recently, Merişor and Beifuss succeeded in getting a phenazine and a benzoxazine by a cyclization reaction that involves a non-conjugated double bond (Scheme 31).[137]



Scheme 31. Synthesis of a tetrahydroquinoxaline and of a dihydro-benzoxazine.

The reaction required very high amounts of catalyst and ligand, still providing only moderate yields of the desired products, in accord with the fact that such a reaction is expected to be very difficult. In the case of the benzoxazine, the catalyst loading could be much decreased with only minor losses in the yield by using ethylene glycol as the solvent at 198 °C.

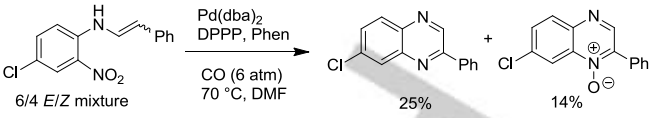
Better results in the synthesis of six-membered rings were obtained by Söderberg by using substrates in which a vinylamine instead of an allylic one is present as a substituent on the nitroarene (Scheme 32).[86]



Scheme 32. Synthesis of dihydroquinoxalines and dihydroquinoxalinones.

We have cited this paper in paragraph 3.2. The initial aim of the work was to prepare *N*-(2-nitrophenyl)imines by condensation of *o*-nitroaniline with different aldehydes and to use them to synthesize benzimidazoles. As previously mentioned, the approach was at least partly successful when a different strategy was employed to prepare the starting imine. However, the direct condensation of *o*-nitroaniline with aliphatic aldehydes only produced the isomerized vinylamines. Palladium-catalyzed reductive cyclization of these compounds, which have only a limited stability, afforded a mixture of dihydroquinoxalines and dihydroquinoxalinones, with the former prevailing most of the times and being the almost exclusive product in a couple of cases. The origin of the oxygen atom in the latter product was initially suspected to be the water present in small amounts under the reaction conditions, but addition of larger amounts of water rather led to the exclusive formation of the dihydroquinoxalines derivative, albeit in a reduced yield. Neither the oxidation of dihydroquinoxaline to dihydroquinoxalinone nor the reverse reduction reaction occurred under the reaction conditions, so that the oxygen atom in the latter compound is very likely to directly derive from the nitro group.

In the only example in which the carbon atom in the *beta* position with respect to the nitrogen atom bore a hydrogen atom, the reaction proceeded up to the quinoxaline in a low isolated yield, accompanied by a lower amount of the corresponding quinoxaline-*N*-oxide (Scheme 33).



Scheme 33. Synthesis of a quinoxaline and of a quinoxaline-*N*-oxide.

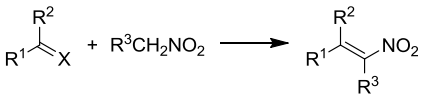
Formation of the latter supports the view that even in this case the cyclization step occurs when the nitro group has been reduced to nitroso and before any further reduction of the latter.

Another reaction leading to the formation of quinolines in competition with indoles has already been described in paragraph 3.1.[87]

4. Synthesis of *N*-heterocycles by *intra*-molecular cyclization reactions of nitroalkenes employing gaseous CO as the reductant

Despite the high selectivities that can be achieved by many of the methods reported in the previous chapter, a limit common to all of them is the preparation of the starting substrates. This can require several synthetic steps and/or expensive starting materials

One of the most interesting innovations in the field of the reductive cyclization of nitroarenes by carbon monoxide in recent years has been the introduction of nitroalkenes as staring materials. This approach requires only one substituent on the arene ring instead of two to effect the cyclization, simplifying the synthetic strategy. The preparation of the starting materials can be straightforward when alkenes having just a substituent on the carbon in the *beta* position with respect to the nitro group are required (R^2 = H in Scheme 34). In such cases, a simple Henry condensation between an aldehyde and a nitroalkane can be efficiently employed.



for R^2 = H, X = O
R^2 = alkyl or aryl, X = NH or $NSiMe_3$

Scheme 34. Synthesis of nitroalkenes.

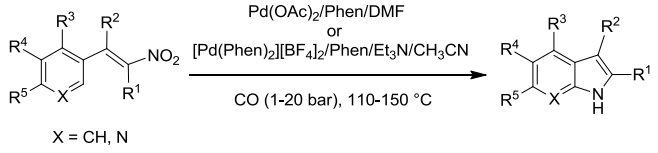
When both R^1 and R^2 are not hydrogen, different strategies can be used for the preparation of the substrates, but those employed up to now involved a condensation reaction between a nitroalkane and an imine featuring a =N-H or =N-$SiMe_3$ group.

The strategy can also be used to prepare pyrroles, when a second double bond is involved in the cyclization instead of an aromatic one. On the other hand, regioselectivity problems can occur in some cases. Since only a few papers have been

published employing this approach, the application to the synthesis of many *N*-heterocycles is still to be explored.

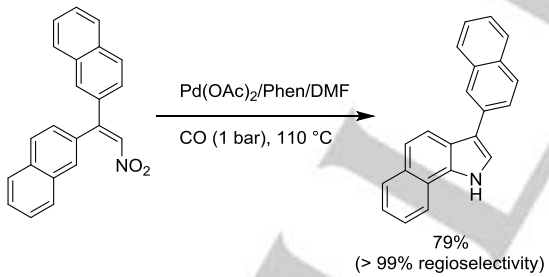
4.1. Synthesis of indoles

Use of β-nitrostyrenes as substrates in a synthesis of indoles using CO as the reductant was first reported by Hsieh and Dong.[138] The reaction was only applied to symmetrical α-aryl-β-nitrostyrenes ($R^1 = R^2 = Ar$, $R^3 = H$ in Scheme 34). Several metal complexes afforded the desired indole, but the best results, up to 98% yield, were obtained employing the $Pd(OAc)_2$/Phen combination under the mild conditions developed by Davies for the cyclization of *o*-nitrostyrenes (1 bar CO, 110 °C, DMF, Scheme 35).[40]



Scheme 35. Synthesis of indoles by cyclization of β-nitrostyrenes.

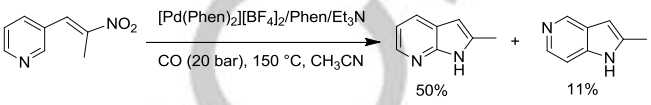
The reaction afforded high yields when the two, equally substituted, aryl rings contained either electronwithdrawing or electrondonating groups in the *para* position. However, the regioselectivity was close to 1:1 for the two possible products when the substituents were initially present in the *meta* position with respect to the vinyl group, except when 1-nitro-2-naphthylethylene was employed as substrate, which provided only one of the two possible isomers with a > 99% regioselectivity (Scheme 36).



Scheme 36. Cyclization of 1-nitro-2-naphthylethylene.

We had independently discovered the same reaction while attempting to use β-nitrostyrenes as substrates for *inter*-molecular amination reactions of olefins (see paragraph 5.1).[139] Our experimental conditions are harsher, 20 bar CO, 150 °C, but they allowed the reaction to be performed even on substrates having a substituent in the *beta* position of the nitrostyrene ($R^1 \neq H$ in Scheme 35), which are unreactive under the experimental conditions employed by Dong. The addition of a weak base, best Et_3N, was found to improve selectivity. Both electronwithdrawing and moderately electrondonating groups on the aryl ring were tolerated, but a methoxy group in the position of R^5 in Scheme 35 decreased the yield and a dimethylamino one completely inhibited the reaction. These results are in accord with the general trends highlighted in paragraph 2.

The reaction could be extended to a pyridine ring having the nitrogen atom in the *meta* position with respect to the nitrovinyl group (Scheme 37).

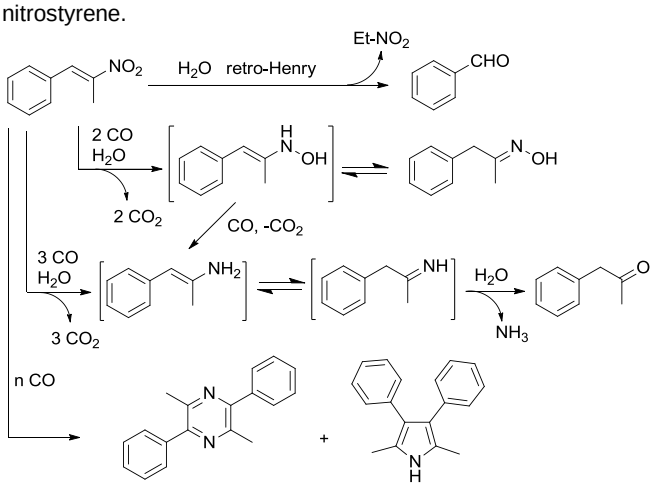


Scheme 37. Cyclization of 1-nitro-2-naphthylethylene.

The result is noteworthy because cyclization of the presumed nitroso intermediate is an electrophilic process, and attack on the electron-poor 2- or 4-position of the pyridine ring should be disfavored. The 80% regioselectivity in 2-methyl-1*H*-pyrrolo[2,3-b]pyridine, the most disfavored product from an electronic point of view, may be ascribed to partial coordination of the substrate to the metal center. On the contrary, reductive cyclization of β-methyl,β-nitro-*m*-chlorostyrene (R^4 = Cl, R^1 = Me) is not regioselective and afforded a *ca.* 1:1 mixture of the two possible products, as observed by Dong for a related substrate.

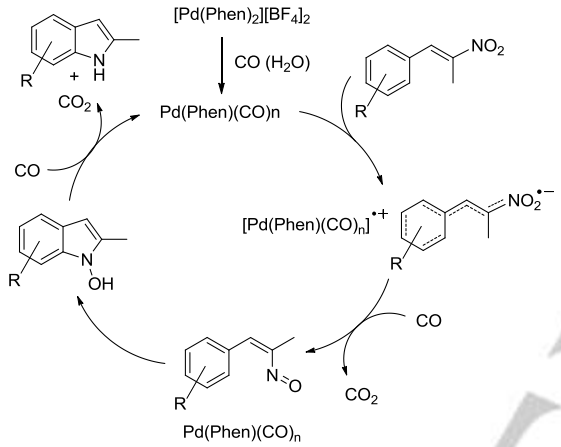
Apart from the dimethylamino-substituted compound mentioned above, the only other substrate for which the reaction failed among those tested was unsubstituted β-nitrostyrene. In this case, the substrate was consumed, but no indole was obtained. This olefin is known to polymerize easily and apparently a substituent either in the *alpha* or in the *beta* position is required to slow down the polymerization to the point that the cyclization reaction can effectively compete with it.

The identity of the byproducts formed in the reaction was investigated by GC-MS (Scheme 38).[139] Three of them derive from reactions involving a hydrolysis of the starting material, whereas two more derive from bimolecular reactions of the nitrostyrene.



Scheme 38. Observed byproducts in the cyclization of β-nitrostyrenes.

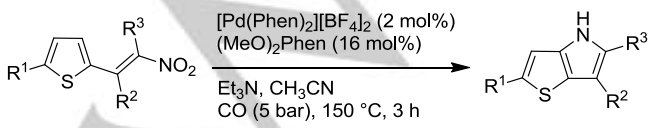
It should be noted that when the Henry reaction is applied to benzaldehyde and its derivatives, it selectively gives the olefin in which the nitro and the aryl group are in a *trans* position. It may appear surprising that the cyclization reaction can occur from this geometry, but the fact that the reaction is efficient is in line with the general trend that the initial activation of the nitro group is an electron transfer from the metal to the nitro compound, generating a transient radical anion. In the present case, charge delocalization is proposed to weaken the double bond character of the alkene moiety and to allow for a rotation of the $–C(R)NO_2$ moiety during the reduction to nitrosoalkene (Scheme 39), leading to the correct geometry for the cyclization step.



Scheme 39. Proposed reaction mechanism for the reductive cyclization of β-nitrostyrenes.

4.2. Synthesis of thienopyrroles

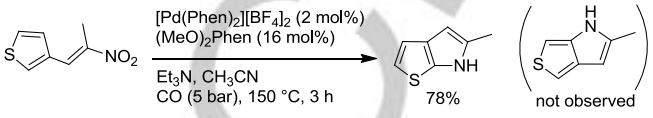
When the same reaction conditions employed for the reductive cyclization of β-nitrostyrenes were employed for the related reaction in which the phenyl ring had been substituted by a thiophene ring, poor yields were obtained. An optimization of the reaction parameters evidenced that the most critical issue is the identity of the ligand. Many different phenanthrolines were tested and best results were obtained with the strongly electrondonating 4,7-dimethoxyphenanthroline (Scheme 40. See also paragraph 2.4 and Scheme 1), in accord with the idea that a nitro group connected to the electrondonating thiophene ring requires a more strongly donating ligand on the metal to be activated.[47]



Scheme 40. Synthesis of thienopyrroles.

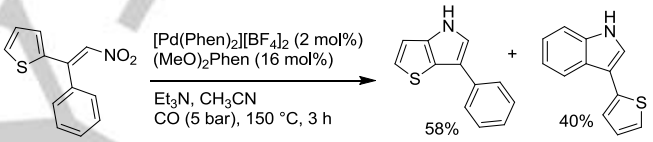
The reaction tolerates reactive groups on the thiophene (R^1 = Br or C≡C-Ph) that may be useful for further functionalization or polymerization in the field of conducting polymers and can be extended to benzo-fused thiophenes as substrates, albeit with a reduced yield.

The nitrovinyl moiety can also be present in the 3 position of the thiophene. In this case, the reaction was regioselective and only the position 2 was reactive (Scheme 41).



Scheme 41. Synthesis of 5-methyl-6*H*-thieno[2,3-*b*]pyrrole.

Reaction of α-phenyl-β-nitrothiophene allowed comparing the reactivity of the phenyl and thiophene rings in the cyclization (Scheme 42).

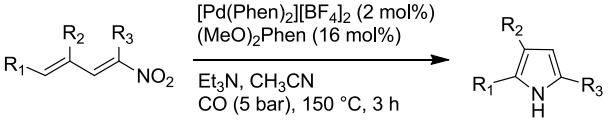


Scheme 42. Competition between a phenyl and a thiophene ring in a cyclization reaction.

Despite the fact that the starting alkene was obtained only as the isomer in which the nitro group is *cis* to the phenyl ring, the reaction yielded a larger amount of the thienopyrrole product with respect to the alternative indole. The selectivity is however low, indicating that the reaction intermediate must be highly reactive.

4.3. Synthesis of pyrroles

Given the ability of nitroso groups to react with alkenes and the possibility of reducing nitroalkenes by CO, a logical extension of the reactivity described above is the cyclization reaction of conjugated nitrodienes. The reaction could indeed be performed by employing the same experimental conditions previously developed for the synthesis of thienopyrroles (Scheme 43).[23]

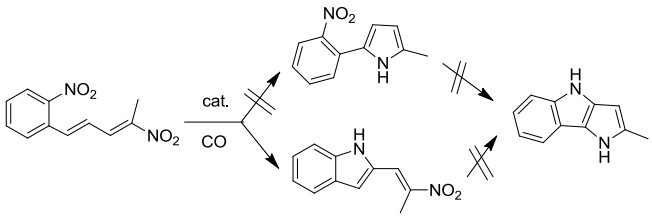


Scheme 43. Synthesis of pyrroles by cyclization of nitrodienes.

This is one of the few syntheses discussed in this review that do not involve an aryl or heteroaryl ring in the reaction. The procedure was applied to the synthesis of several di- and tri-substituted pyrroles.

When R^1 is an aryl ring, both electrondonating and electronwithdrawing groups were well tolerated, including the very electrondonating dimethylamino one, whose presence inhibited the reaction in most other cases. The long distance between the substituent and the reacting nitro group is likely responsible for the little sensitivity of the reaction to the electrondonating power of R^1. For the same reason, R^1 could also be a pyrrole, a furan, or a thiophene ring.

Use of a substrate having both a nitro group directly bound to an aryl ring and another one bound to the diene fragment allowed comparing the reactivity of the two (Scheme 44).



Scheme 44. Competition between a nitroarene and a nitrodiene in the cyclization reaction.

Not unexpectedly, given the harsher conditions required to effect the cyclization of nitroalkenes with respect to *o*-nitrostyrenes, the reaction exclusively afforded the indole derivative. Furthermore, the indole ring so formed is donating enough to deactivate the nitroalkene and to inhibit a second cyclization reaction.

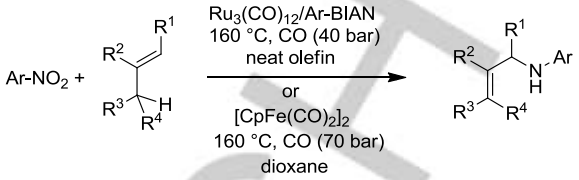
5. Synthesis of *N*-heterocycles by *inter*-molecular cyclization reactions of nitroarenes and alkenes or alkynes employing gaseous CO as the reductant

All reactions described in the previous paragraphs require the preparation of a specific substrate. Developing *inter*-molecular reactions can clearly be advantageous to minimize the number of synthetic steps and allow a faster access to a library of derivatives. Only a few cases of such a reactivity have been reported and these are described in the following.

5.1. Synthesis of allylic amines from nitroarenes and unfunctionalized alkenes

Allylic amines are not heterocyclic compounds, but are briefly discussed here because the development of their synthesis led to catalysts that have later been employed for the synthesis of compounds that are relevant to this review.

Allylic amination of unfunctionalized alkenes by nitroarenes and CO was first reported to be catalyzed by $Ru_3(CO)_{12}$ in the presence of Ar-BIAN ligands (Scheme 45, see also Scheme 1).[26, 140-141]



Scheme 45. Synthesis of allylic amines.

The reaction is most effective when nitroarenes bearing electronwithdrawing groups are employed and could be applied to cyclic olefins or to α-methylstyrene, but linear aliphatic olefins failed to give the allylic amine. Ar- BIAN ligands, best 4-$CH_3C_6H_4$-BIAN were instrumental in affording high selectivities. Phenanthroline gave a high reaction rate, but a low selectivity. Noteworthy, a palladium/phenanthroline catalyst only afforded trace amounts of allylic amine. The main defect of this reaction is that the alkene must be employed in a large molar excess, best as the solvent.

A mechanistic study[26] showed that the reaction proceeds by the intermediate fragmentation of the cluster to give Ru(Ar-BIAN)$(CO)_3$, which is in equilibrium with the olefin complex Ru(Ar-BIAN)$(CO)_2$(alkene). The latter reacts with the nitroarene in the rate-determining step of the catalytic cycle.

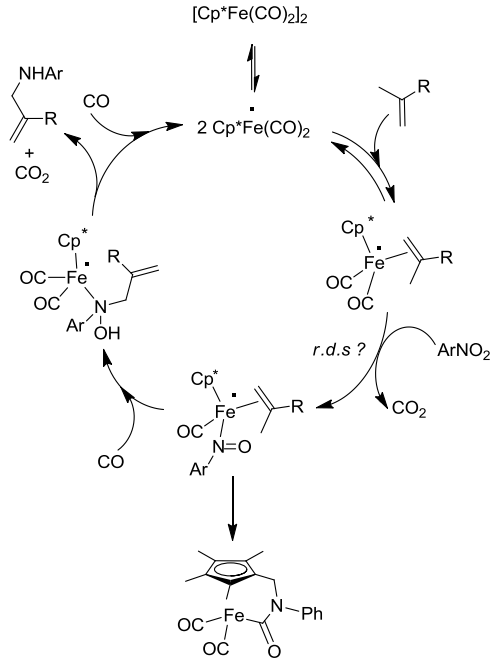
Nicholas and coworkers developed the use of the iron-cyclopentadienyl complex, $[CpFe(CO)_2]_2$ to catalyze the same reaction (Scheme 45).[142] The iron catalyst is less active than the ruthenium one, but has the advantage of requiring only a 30 mol-% excess of the alkene with respect to the nitroarene to be employed.

Both with the ruthenium and the iron catalysts, the reaction proceeds by an attack to the less hindered olefinic carbon, followed by a transposition of the double bond. It is not the allylic C-H bond to be activated directly.

The pentamethylcyclopentadienyl analogue $[Cp^*Fe(CO)_2]_2$ could also be employed as catalyst under the same experimental conditions.[143] Moreover, the reaction was also performed under near UV irradiation (λ > 300 nm).[144] $[CpFe(CO)_2]_2$, $[Cp^*Fe(CO)_2]_2$, and $[Cp^*Ru(CO)_2]_2$ were tested as catalyst. Best results were obtained with $[Cp^*Fe(CO)_2]_2$. Yields were most of the times lower under UV irradiation than under standard conditions, but the reaction could be performed at lower pressures and temperatures (3-6 atm, 120 °C) and in a glass autoclave.

During the period covered in more detail in this review, the mechanism of the iron-catalyzed reaction was investigated.[95] The kinetics of the $[CpFe(CO)_2]_2$-catalyzed allylic amination of substituted α-methylstyrene derivatives by nitroarenes was found to be first-order in both alkene and nitroarene, zero-order in CO, and half-order in catalyst. Relative rate studies of *para*-substituted α-methylstyrenes and nitroarenes evidenced a rate increase for electron-deficient nitro compounds and for electron-rich alkenes. Attempts to trap free nitrosobenzene by reaction

with a conjugated diene (see also later) failed and reaction of *o*-nitrobiphenyl yielded the allylic amine and not carbazole. Based on these results, a reaction mechanism was proposed, which bear many similarities to that proposed for the $Ru_3(CO)_{12}$/Ar-BIAN catalytic system (Scheme 46).



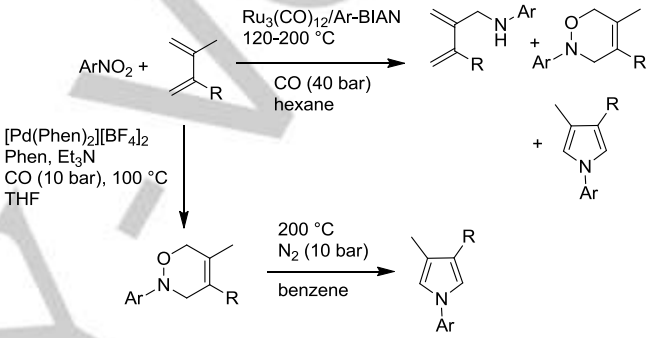
Scheme 46. Proposed reaction mechanism for the $[CpFe(CO)_2]_2$-catalyzed allylic amination of alkenes.

The dimeric precatalyst is in equilibrium with the monomeric species, which is the actual catalyst. This reversibly coordinates the olefin before the rate-determining reaction with the nitroarene, which affords a complex with a coordinated nitrosoarene. Coupling of the coordinated nitrosoarene and olefin, with transposition of the double bond, generates a coordinated allyl hydroxylamine, which is finally reduced to the amine by CO, with regeneration of the active catalyst. When the catalyst contain the pentamethylcyclopentadienyl ligand instead of the unsubstituted Cp, it had been earlier found that deactivation can occur by the formation of a complex in which a methyl group of the ligand has been aminated.[143] On the other hand, the nitrosobenzene complex $[CpFe(CO)_2(\kappa_1\text{-}N\text{-}PhNO)][BF_4]$, prepared by reaction of $[CpFe(CO)_2I]$ with nitrosobenzene and $AgBF_4$, was found to afford only trace amounts of allylic amine and is not an active intermediate in the catalytic cycle.[145]

The application of the $[Cp^*Fe(CO)_2]_2$-catalyzed photostimulated reaction was also extended to some cyclic olefins (cyclopentene, cyclohexene, cyclooctene).[146] By comparison with the results previously obtained by using the same catalyst, it appears that the reaction of internal olefin is most of the times slower than that of terminal ones, although the selectivity in allylic amine is equally good.

5.2. Synthesis of oxazines and *N*-arylpyrroles from nitroarenes and unfunctionalized dienes

The addition of a conjugated dienes to a reaction mixture is a classical test to check the formation of free nitrosoarenes during the reaction, as these are quickly trapped by the diene in a hetero Diels-Alder reaction to give oxazines. When we tested the use of 2,3-dimethylbutadiene as substrate in the $Ru_3(CO)_{12}$/Ar-BIAN catalyzed allylic amination reaction, both the allylic amine and the oxazine were obtained, accompanied by some *N*-arylpyrrole, whose amount increased at higher reaction temperatures (Scheme 47).[27] Pyrroles derive from a dehydration of the oxazine, a reaction that is also apparently catalyzed by the ruthenium catalyst.



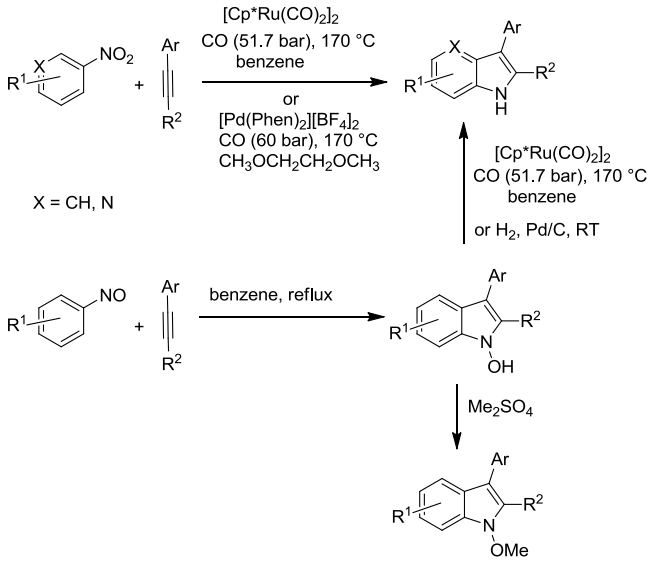
Scheme 47. Synthesis of allylic amines, oxazines and *N*-arylpyrroles by reaction of nitroarenes with conjugated dienes.

The reaction between a nitroarene and a diene can be made selective towards the formation of the oxazine by employing a palladium/phenanthroline catalyst and working at a relatively low temperature, 100 °C.[69] If desired, the obtained oxazine can then be thermally converted to the pyrrole in one pot by heating at 200 °C. Carbon monoxide is not required for this step and a dinitrogen pressure can be employed to avoid the boiling of the solvent.

No advancement in the use of gaseous CO for these reactions has been reported recently, but the use of phenyl formate as a CO surrogate for the synthesis of oxazines has been very recently reported and will be discussed in paragraph 6.2

5.3. Synthesis of indole from nitroarenes and alkynes

While attempting to extend the allylic amination strategy described in paragraph 5.1 to the synthesis of propargylic amines, Penoni and Nicholas discovered a new reaction, which affords indoles instead of the expected amines (Scheme 48).[147] The reaction is catalyzed by the same dimeric cyclopentadienyl complexes found to catalyze the allylic amination reaction, but in this case the best results were obtained by the use of $[Cp^*Ru(CO)_2]_2$. The alkyne must be connected to an aryl group in order for the reaction to proceed and is regiospecific. The aryl group is only found in the position 3 of the formed indole. Aliphatic alkynes only afforded trace amounts of indole.



Scheme 48. Synthesis of indoles, *N*-hydroxyindoles and *N*-methoxyindoles by reaction of alkynes with nitro- and nitrosoarenes.

The same products are obtained when nitroarenes are replaced by nitrosoarenes.[24] By employing these substrates, it could be shown that the reaction between a nitrosoarene and an aryl alkyne occurs even in the absence of any catalyst, to give *N*-hydroxyindoles. The latter can be reduced in a separate step either by CO in the presence of $[Cp^*Ru(CO)_2]_2$ or even by H_2 with Pd/C as catalyst. The selectivity of the reaction is not high (max 53% from a nitroarene and 64% from a nitrosoarene), but the synthetic strategy is very simple and affords the indole in one step from simple starting materials.

Following this report, we tested the use of the palladium/phenanthroline catalytic system for the same reaction and we found it to work very well (Scheme 48). The selectivity in indole was not improved, but under comparable experimental conditions, the palladium catalyst is about 500 times more active than the ruthenium one, allowing for the use of much lower catalyst amounts and shorter reaction times.[96]

The reaction tolerates both electronwithdrawing and electrondonating substituents on the nitroarene and also on the alkyne ring, including in the latter case a free amino group, which would not be tolerated by many indole syntheses. At least when the palladium catalyst is employed, the kinetics is first order in the nitroarene and the reaction is faster when electronwithdrawing groups are present on the nitroarene, consistent with a rate-determining activation of the nitro group by an electron transfer from the metal, as discussed in section 2. However, the selectivity in indole is also a function of radical-stabilization effects indicating the accumulation of unpaired spin density at some stage of the reaction. On the other hand, substitution of $PhNO_2$ by $PhNO_2$-d_5 or use of a mixture of the two led to almost indistinguishable results with respect to both reaction rate and indole selectivity, indicating that C-H activation is fast compared to other steps of the cycle.

When nitrosoarenes are employed as substrates, the aryl ring in the alkyne can be replaced by a -COOMe group, maintaining the same regioselectivity.[24] However, dimethylacetylenedicarboxylate completely inhibited at least the palladium-catalyzed reaction. Since this alkyne is known to dimerize in the presence of palladium complexes with chelating nitrogen ligands, it is likely that a related reactivity is involved here.[148]

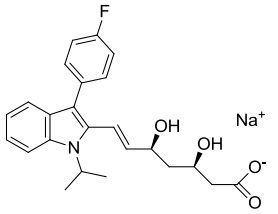
During the period investigated in more detail in this review, Penoni and Nicholas argued that a weak point of the synthetic strategy is the accumulation of *N*-hydroxyindoles during the reaction, since such compounds are very reactive and can enter several secondary reactions, including dimerization.[149] The solution they found was to react the nitrosoarene with the alkyne in the presence of an alkylating agent, dimethyl sulfate or methyl iodide, and this allowed obtaining better yields of *N*-methoxyindoles (Scheme 48). The latter can be converted to the corresponding indoles by the same methods found to be efficient for the reduction of *N*-hydroxyindoles.

This report stimulated us to find a way of accelerating the consumption of *N*-hydroxyindoles even during the catalytic reaction employing nitroarenes as substrates.

No specific study has been devoted to the reduction of *N*-hydroxyindoles, but analogies with the synthesis of anilines by reduction of nitroarenes by CO/H_2, where hydroxylamines are likely to be formed, suggest that ruthenium complexes should be more active catalysts for this reaction than palladium ones.[1, 58] The approach was partly successful and the addition of $Ru_3(CO)_{12}$ to the catalytic system in a 1-1.5 mol ratio with respect to palladium increased the selectivity in indole by 8-11%.[150] The ruthenium cluster alone was found not to catalyze the reaction under these conditions, even when activated by Ph-BIAN as a ligand, supporting the idea that it plays a role only after the initial activation of the nitroarene has been performed by palladium. Surprisingly, the addition of Ph-BIAN to the catalytic system when both metals are present decreased the selectivity, despite the fact that it strongly promotes the activity of $Ru_3(CO)_{12}$ in the reduction of nitroarenes by CO/H_2O.[60, 151]

As a second approach, we also tested the addition of alkylating agents. Dimethylsulfate was deemed to lead to methylation of phenanthroline and indeed completely deactivated the palladium catalyst. However, the weaker alkylating agent dimethylcarbonate improved the selectivity, albeit by only 8 %.[150] Interestingly, the two approaches could be employed together, affording an absolute increase in selectivity of 16 % (36 % if measured with respect to the obtained indole).

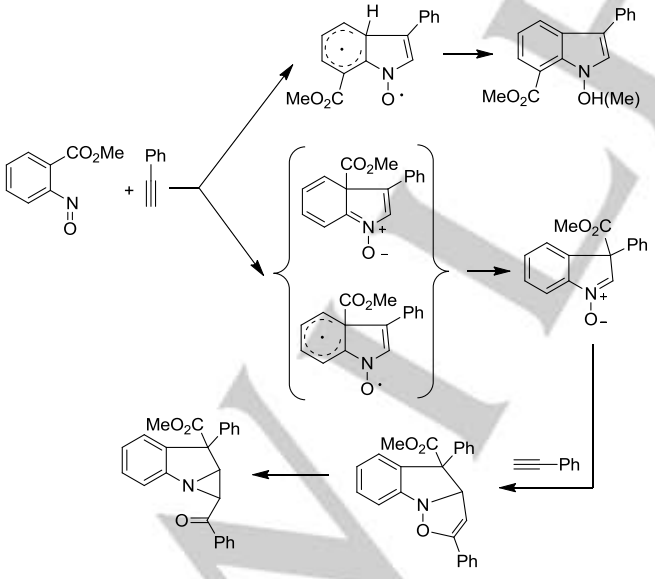
The approach was particularly effective for the reaction of nitrobenzene with 4-fluorophenylacetylene to give 3-(4-fluorophenyl)indole. This indole constitutes the skeleton of several pharmaceutically active compounds, among which Fluvastatin (Lescol®, a cholesterol lowering agent, Scheme 49) is that produced on the largest scale. It was obtained in a 71% yield by the addition of both $Ru_3(CO)_{12}$ and dimethylcarbonate, whereas the yield was only 37% in their absence.



Scheme 49. Fluvastatin.

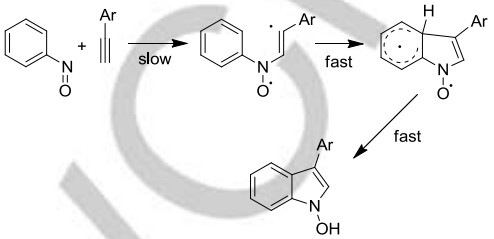
The mechanism of the reaction between nitrosoarenes and alkynes has been investigated by both experimental and computational methods.[152] The reaction between nitrosobenzene and phenyl acetylene is first order in each reactant and the reaction is accelerated both by electronwithdrawing groups on the nitrosoarene and donating groups on the aryl alkyne. The kinetic isotope effect is close to 1. All of these results paralleled those previously observed for the reactions starting from nitroarenes,[24, 96, 150] strongly supporting the idea that the latter are intermediately reduced to nitrosoarenes and that the cyclization reaction occurs at this stage of the reduction process in both cases. The only difference is that in the case of nitroarenes the rate-determining step of the reaction is the initial activation of the nitro group, which is even slower than the reaction between the corresponding nitrosoarene and the alkyne.

As a further mechanistic hint, the reaction between *o*-carbomethoxy-nitrosobenzene and phenyl acetylene afforded, in addition to 3-carbomethoxy-*N*-hydroxyindole or its *N*-OMe analogue, a tricyclic indole derivative, which appears to derive from the trapping of an intermediate indoline nitrone by phenyl acetylene and subsequent rearrangement (Scheme 50).[152]



Scheme 50. Formation of a bicyclic product from the reaction of *o*-carbomethoxy-nitrosobenzene with phenyl acetylene.

Theoretical calculations reproduced well the experimental results and added details to the reaction mechanism. The reaction initially generates a diradical species, which rapidly evolves by activation of the aromatic C-H bond to give a nitrone. The latter finally tautomerizes to the *N*-hydroxyindole (scheme 51). More details on the steps involved in the cyclization can be found in the original paper.[152]



Scheme 51. Mechanism of the reaction between nitrosobenzene and aryl alkynes.

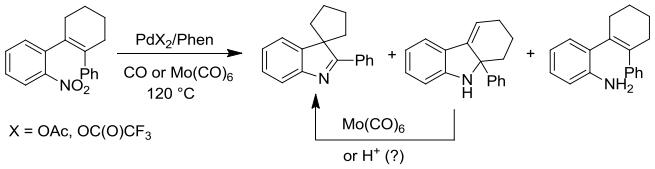
Several papers have been published on synthetic applications of the reaction between nitrosoarenes and alkynes.[153-158] These are outside the scope of this review and the interested reader is referred to the cited literature.

6. Use of CO surrogates as reducing agents

Despite the high efficiency of several of the reactions described in the previous paragraphs, their use has not spread outside the limited number of groups that reported them. This is likely mostly due to the need for pressurized CO, which in turn requires safety measures that are not available in most synthetic organic laboratories. This problem is common to other carbonylation reactions and in recent years much attention has been given to the use of CO surrogates. These are molecules that can liberate carbon monoxide in the same vessel in which the catalytic reaction is performed or be employed in a two-chambers reactor, where the CO generation reaction occurs separately from the carbonylation one.[159-169]

6.1. $Mo(CO)_6$ as a CO surrogate

The first report to be published on the use of a CO surrogate in the field covered by this review was a paper by Driver. In that work, the synthesis of some 3*H*-indoles starting from suitably substituted nitrostyrenes was catalyzed by palladium/phenanthroline complexes in the presence of $Mo(CO)_6$.[25] α,β,β-Trisubstituted-*o*-nitrostyrenes in which the C=C double bond is part of a cyclic system were employed. Such compounds cannot give a fully aromatic indole and the synthesis of spirocyclic compounds was targeted. The reaction was first optimized employing a phenyl-substituted nitrostyrene as substrate (Scheme 52).

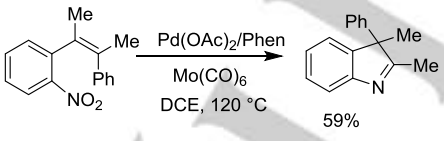


Scheme 52. Synthesis of spirocyclic 3*H*-indoles.

Use of the $Pd(OAc)_2$/Phen catalytic system under 1.5 atm CO and at 120 °C in DMF allowed the reaction to proceed, but the main product was the indoline. The formation of this byproduct could be suppressed by replacing palladium acetate with palladium trifuoroacetate and by working in the presence of trifluoroacetic acid. The yield in the desired spirocyclic product only reached 62% anyway. On the other hand, when $Mo(CO)_6$ was employed as the CO source, no indoline was formed, although a relatively large amount of the aniline was obtained when using DMF as solvent. However, none of these two byproducts was formed when the $Pd(OAc)_2$/Phen catalytic system was employed with $Mo(CO)_6$ as the CO source and in dichloroethane (DCE) as solvent, affording the spirocyclic compound in 80 % yield. It was independently proved that $Mo(CO)_6$ catalyzes the isomerization of the indoline to the spirocyclic indole. No test was reported on the effect of acids on the same transformation, although from the results obtained, it is likely that acids also catalyze this transformation.

The reaction could be extended to nitroarenes bearing either electronwithdrawing or electrondonating groups and to compounds were a different aryl or even a methyl group are present in place of the phenyl substituent.

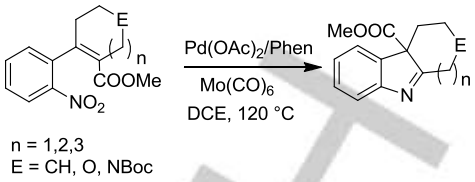
In light of what said in paragraph 3.1 on the relative migrating attitude of aryl and alkyl groups in the cyclization reaction of β,β-disubstituted-*o*-nitrostyrenes, it may appear surprising that the alkyl substituent migrates in preference to the aryl one in this system. However, when a substrate in which the double bond is not part of a cycle was employed, the regular outcome was observed (Scheme 53).



Scheme 53. Selective migration of the phenyl ring in an open system.

Thus, the formation of the spirocyclic compound must be due to stability effects specific of these cyclic products rather than to a peculiarity of the catalytic system employed.

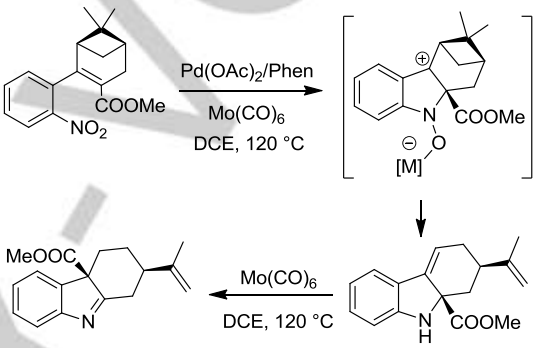
The identity of the product is anyway a sensitive function of the migrating group. When the phenyl group in the substrate was replaced by a carbomethoxy one, only migration of the latter and no ring contraction was observed (Scheme 54).



Scheme 54. Selective migration of the carbomethoxy group.

The reaction was also applied to substrates in which a larger ring is present or the ring contains a heteroatom.

A first clue on the reaction mechanism came from the reaction of a pinene-derived substrate (Scheme 55).



Scheme 55. Stepwise synthesis of pinene-derived 3*H*-indole.

In this case, the reaction initially afforded an indoline, which isomerized to the final 3*H*-indole only upon further treatment with $Mo(CO)_6$, supporting the intermediate formation of the former in the synthesis of the latter. Furthermore, a ring opening of a pinene ring is consistent with the formation of a positive charge on the benzylic carbon during the cyclization reaction.

Additional experiments were run in order to elucidate the reaction mechanism.

Reaction of a nitroarene having in the *ortho* position an alkyl chain instead of an alkene only provided the corresponding aniline. Failure to get any cyclized product is considered an evidence against the formation of nitrenes as intermediates, since the latter should activate even C-H bonds on sp^3 carbon atoms.

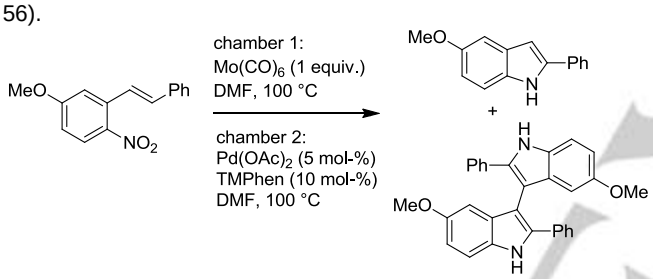
Attempts to trap an intermediately formed nitrosoarene by reaction with a conjugated diene to give an oxazine (see paragraphs 5.2 and 6.2) also failed, but in our view this should not imply that nitrosoarenes are not formed because the *intra*-molecular reaction of the nitrosoarene with an alkene is likely to be faster than any *inter*-molecular reaction.

The reaction of an independently prepared nitrosoarene with 2,3-dimethylbutadiene under typical reaction conditions (120 °C, DCE) obviously provided the oxazine, but, interestingly, the addition of $Mo(CO)_6$ to the reaction mixture completely blocked the hetero Diels-Alder reaction. It is clear that $Mo(CO)_6$ intercepts nitrosoarenes at a faster rate than 2,3-dimethylbutadiene does.

$Mo(CO)_6$ (1 equiv.) could promote the reaction even in the absence of any palladium, but the yield was only 20%.

Together, these data led to the proposal of a reaction mechanism in which palladium is involved in the initial reduction of the nitro to nitroso group, whereas the following stages on the way to the indoline may involve the participation of either palladium or molybdenum. The final isomerization is surely catalyzed by a molybdenum complex, so that $Mo(CO)_6$ does not act only as a CO source in this system. The possibility that the actual catalyst is a Pd-Mo bimetallic species was also considered as an alternative.

The non-innocent role of $Mo(CO)_6$ is also indicated by the fact that when the procedure was applied to a nitrostyrene that may yield the fully aromatic indole, α-phenyl-*o*-nitrostyrene, less than 20% of the latter product was obtained.[128] It was necessary to perform the reaction in a two-chamber reactor, where the decomposition of $Mo(CO)_6$ is separated from the palladium-catalyzed cyclization reaction, in order to get good yields of the indole. The reaction conditions were optimized by employing 4-methoxy-β-phenyl-2-nitrostyrene. Use of the same experimental conditions optimized for the synthesis of the spirocyclic compounds gave a 1:1 mixture of indole and bis-indole (Scheme 56).

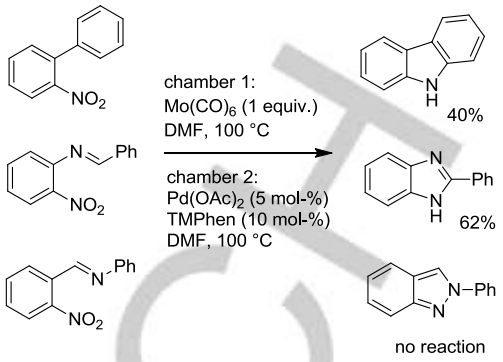


Scheme 56. Indole and bis-indole obtained by employing $Mo(CO)_6$ as a CO surrogate.

The yield in indole could be improved by the use of TMPhen as a ligand and by operating under more diluted conditions at a slightly lower temperature (100 instead of 120 °C). Under these conditions, a 96:4 ratio indole/bis-indole could be reached. Use of DMA as the solvent gave results indistinguishable from those obtained working in DMF, whereas DMSO gave a better selectivity in indole vs. bis-indole, but a lower absolute yield. No reaction was observed in DCE.[128] $Cr(CO)_6$ and $W(CO)_6$ were also tested as CO surrogates, but gave worse results.

The reaction could be applied to nitroarenes bearing both electrondonating and electronwithdrawing substituents and to differently substituted alkene moieties. The presence of a methyl group on the *ortho* position with respect to the nitro group was also tolerated, although the yield was reduced to 48%.

The optimized protocol was also tested on the synthesis of carbazoles, benzimidazoles and indazoles (Scheme 57).[128]



Scheme 57. Use of $Mo(CO)_6$ as a CO surrogate in the synthesis of other heterocyclic compounds.

The first two reactions did produce the desired product, albeit in a lower yield than that achieved for most indoles, but the latter failed. We have already commented in paragraph 3.2. on the difficulty of obtaining indazoles by cyclization reactions of nitroarenes.

6.2. Formate esters and salts as CO surrogates

We also independently considered the problems associated with the use of gaseous CO and started an investigation of a suitable CO surrogate that may also be employed on a small scale industrial production. Among all those reported, we chose to employ formate esters because of their commercial availability, low cost and low toxicity. Note that, on the other hand, $Mo(CO)_6$ is very toxic and costly, so that its use is limited to a laboratory scale. We also selected the Pd-catalyzed synthesis of indoles from *o*-nitrostyrenes as the first reaction to test and chose to operate in a single glass pressure tube because this equipment is cheap and available in different sizes.[170] A steel autoclave can also be used, but without the need for pressurized CO.

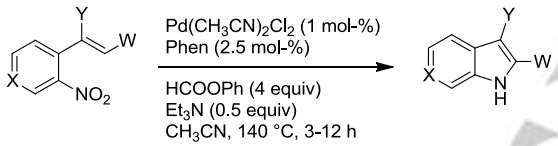
Alkyl formates were initially tested because their low cost allows them to be employed even as solvents. Activation of alkyl formates can be effected by different means, including very strong bases, but $Ru_3(CO)_{12}$ in the presence of phenanthroline was chosen among them because of its compatibility with the cyclization reaction here investigated.[171-173] The $Ru_3(CO)_{12}$/Phen catalytic system was found to be able to catalyze the reductive cyclization of nitrostyrenes using *n*-butyl formate as the CO surrogate even in the absence of any palladium source, but the reaction was slow. On the other hand, a palladium catalyst alone, even if in the presence of a weak base, was completely ineffective, confirming the idea that a ruthenium complex is needed to activate alkyl formates. Better results were obtained by the combined use of $Ru_3(CO)_{12}$, $[Pd(Phen)_2][BF_4]_2$, Phen and Et_3N, but a high temperature, 180 °C, was still needed and selectivities in indole were only moderate to good (52-70%) depending on the substrate.

Stimulated by recent results in the literature showing that aryl formates are activated more easily than alkyl ones,[167-168, 174-178] we tested the use of phenyl formate and found that better results can be obtained under milder conditions. Moreover, only a slight

excess of formate is required to consume all the nitroarene (3.4 fold the stoichiometric amount with respect to the required CO) and there is no need to add a ruthenium catalyst. Control experiments showed that it is the base (Et_3N) that activates the formate (first order kinetics in both phenyl formate and Et_3N), whereas the palladium catalyst is unable to decompose it.

The reaction conditions were optimized using o-nitro-methylcinnamate. Several palladium precatalysts ($[Pd(Phen)_2][BF_4]_2$, $Pd(OAc)_2$, $Pd(CH_3CN)_2Cl_2$, $Pd(dba)_2$) gave good results, but $Ru_3(CO)_{12}$ gave a much slower and less selective reaction. Among the palladium precursors, $Pd(CH_3CN)_2Cl_2$ was the one that afforded best results (> 99% conversion, 98% selectivity). This is surprising as chlorides usually inhibit the activity of palladium/phenanthroline complexes in reductive carbonylation reactions of nitroarenes because of the formation of the little soluble $Pd(Phen)Cl_2$.[36] However, there are a few cases in which the addition of small amounts of chloride was found to be positive and the effect attributed to the formation of zerovalent anionic palladium complexes in which chloride is bound to the metal and increases the electron density on it,[66] analogously to what is well established for palladium-phosphine complexes.[179-180]

The reaction scope was explored and good to excellent yields, up to 98% were obtained in most cases (Scheme 58).



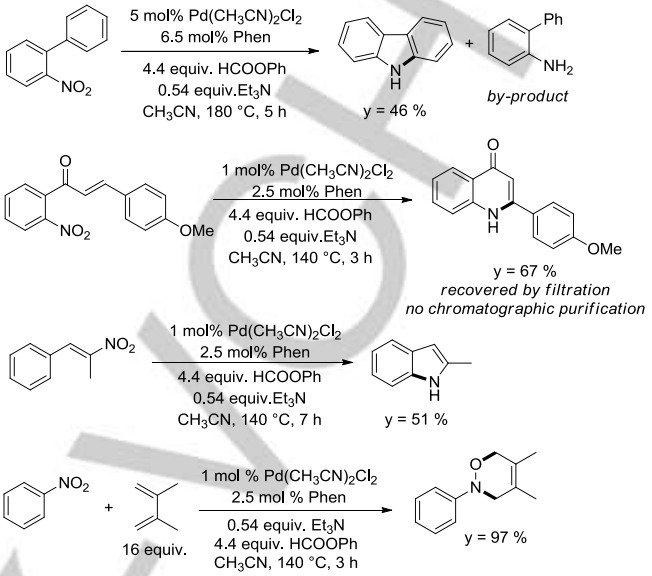
X = CH, CMe, CCl, CBr, CCF_3, N
Y = H, CN, COOMe
W = H, Ar, Py, COOR, $CONR_2$, C(O)Ph, CHO

Scheme 58. Synthesis of indoles using phenyl formate as a CO surrogate.

Esters and amides derived from 2-nitrocinnamic acid were successfully cyclized and. indoles substituted in the 2 and 3 positions with aryl, 2-pyridyl and cyano groups were also successfully obtained in excellent yields. Labile bromo, chloro and aldehydic groups were well-tolerated. Noteworthy, 2-phenyl-6-azaindole was synthetized in very high yield (91%).

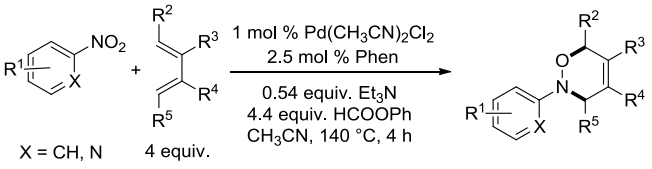
A comparison between a reaction run in the presence of phenyl formate and one conducted under the same conditions, but without formate and working under CO pressure (30 bar) showed that the reaction with the formate is not only faster, but even more selective. In general, it was found that in all cases in which the produced indoles had been previously obtained by a reductive carbonylation of nitroarenes working under CO pressure, the yields obtained by our protocol were higher than the best yield previously reported for the same indole.

The developed protocol was tested on other related reactions, featuring respectively the functionalization of an aromatic C-H bond,[38] the formation of a six-membered ring,[135] the cyclization of a β-nitrostyrene,[139] and an *inter*-molecular cyclization reaction[27, 69] (Scheme 59). The protocol worked in all cases despite the fact that experimental conditions were not optimized for these specific reactions.



Scheme 59. Application of the HCOOPh protocol to the synthesis of other heterocycles.

The synthesis of 3,6-dihydro-2*H*-[1,2]-oxazines was then independently investigated in more detail.[100] Given the excellent result obtained in the single experiment performed, the same experimental condition previously optimized for the synthesis of indoles were employed, but the amount of diene was optimized. The excess diene could be decreased from 16 equivalents with respect to the nitroarene to 4 with minimal variations in the isolated yield (96% against 97%) and this amount was employed in the investigation of the substrate scope (Scheme 60).



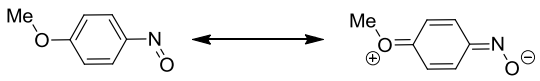
Scheme 60. Synthesis of oxazines by reaction of nitroarenes and conjugated dienes, employing HCOOPh as a CO surrogate.

The tolerance to substituents on the nitroarene ring was investigated by employing 2,3-dimethylbutadiene as the reference diene ($R^3 = R^4 = Me$, $R^2 = R^5 = H$ in Scheme 60). 4-Fluoro, chloro, bromo, and trifluoromethyl-substituted nitrobenzene gave the corresponding oxazine in almost quantitative yield. This was not an obvious results because palladium/phenanthroline complexes are known to catalyze the Heck reaction.[181] Thus, a competitive activation of the carbon-halogen bond may have occurred, at least in the case of the bromo derivative. The bromo substituent could also be present

in the *ortho* position with respect to the nitro group, indicating a good tolerance of the reaction to steric hindrance.

Among other electronwithdrawing groups, methoxycarbonyl (-COOMe) was also well tolerated, but a carboxamido (-$CONH_2$) substituent gave a low 25% yield. Here a competitive reaction can occur because nitroarenes are readily carbonylated to diaryl ureas when reacted with arylamines,[1, 4, 7, 21, 67-68] a reaction that is efficiently catalyzed by palladium/phenanthroline complexes,[65-66] and amides have been shown to be able to enter this reaction in place of amines, affording acyl ureas.[182]

A free –COOH group was partly converted to its phenyl ester by reaction with the phenol liberated during the formate decomposition. Moderately donating alkyl groups were well tolerated, but a strongly donating methoxy group was not. We have already commented on the activation of nitroarenes by an electron transfer, which is made more difficult by strongly donating substituents on the aryl ring. Additionally, the presence of a *para* methoxy group on the aryl ring of nitrosobenzene allows a quinonoid resonance form, where the nitroso group gain a negative charge and loses its double bond character, making it unsuitable to undergo a Diels-Alder reaction (Scheme 61).[183]

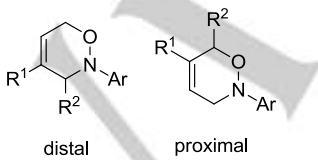


Scheme 61. Resonance forms of 4-nitrosoanisole.

Interestingly, the protocol was compatible with the presence of two functional groups, cyano and formyl, which may themselves be involved into a Diels-Alder reaction. In particular, tolerance of the formyl group is noteworthy because the oxazine containing this substituent would likely not be obtainable starting from the corresponding aniline under oxidizing conditions, an alternative strategy for the formation of this kind of heterocycle.

As far as heteroaromatic nitro compounds are concerned, the electron poor pyridine ring (X = N in Scheme 60) allowed the reaction to proceed efficiently, but the electron rich thiophene did not.

When dienes not substituted in a symmetric way are used as substrates, two isomers (distal and proximal) can be obtained (Scheme 62).



Scheme 62. Distal and proximal isomers of 3,6-dihydro-2*H*-[1,2]-oxazines.

Both isomers were obtained in all cases, with the distal isomer prevailing when the substituent is present on the internal position of the diene ($R^1 \neq H$, $R^2 = H$), and the proximal prevailing when the substituent is present in the terminal position of the diene ($R^1 = H$, $R^2 \neq H$). This is in qualitative agreement with what reported in the literature for the hetero Diels-Alder reaction of the same dienes with nitrosoarenes.[184-185] Moreover, a very close product distribution was observed after a catalytic reaction involving nitrobenzene and isoprene on one side and a stoichiometric reaction involving nitrosobenzene and the same diene and run in the same solvent and at the same temperature on the other. This suggests, even if does not definitely proves, that the hetero Diels-Alder reaction is occurring while none of the two reagents is coordinated to palladium.

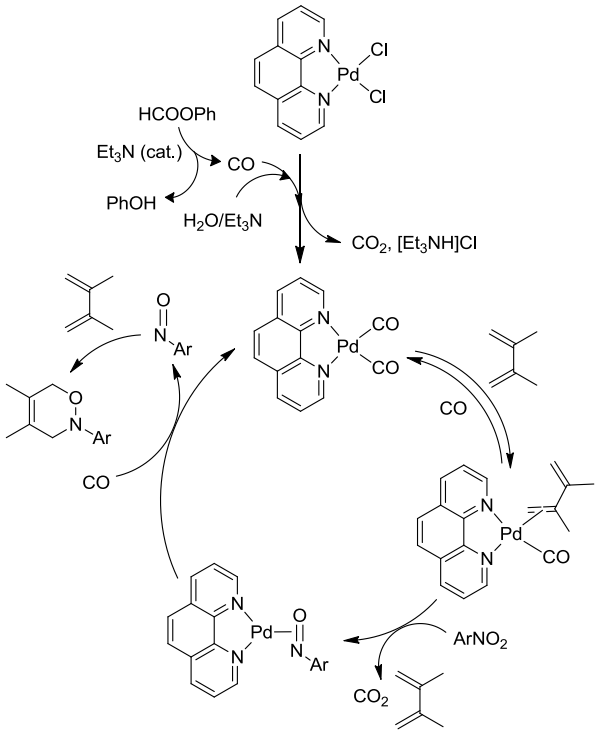
2,3-Dimethoxydiene and unsubstituted butadiene also gave the oxazine, but dienes bearing two substituents on the 1 and 4 positions of the diene fragment did not give any oxazine. In these cases, the formation of the hetero Diels-Alder adduct is reversible at high temperature and the so formed free nitrosoarene can enter competitive reactions.

Since, depending on the respective substitution patterns, dienes can be more expensive than nitroarenes, we also performed a reaction in which a twofold excess of nitroarene was present with respect to the diene. The desired oxazine was again obtained, although with a somewhat reduced yield of 68%.

With the exception of the reaction run in the presence of an excess nitroarene, the yield obtained by the formate protocol are always higher than those previously obtained by performing the same reaction under CO pressure and this includes the results obtained employing the palladium/phenanthroline system.[69]

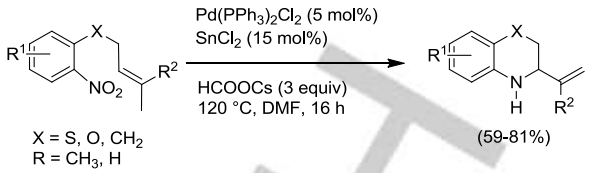
Moreover, except for the cases in which the present protocol failed, the yields obtained employing it are, to the best of our knowledge, always higher than those obtained by direct reaction of the corresponding nitrosoarenes with dienes. It may appear odd that a higher yield is obtained by generating nitrosoarenes *in situ* than by using the pure compounds. However, nitrosoarenes are in equilibrium in solution with their dimeric form and the dimer is not inactive. Generating the nitrosoarene slowly during the reaction can minimize dimer formation.

As far as the reaction mechanism is concerned, it was noted that when sterically hindered dienes are employed as substrates, not only is the oxazine not formed, but even the nitroarene conversion is much lower. This implies that the diene accelerates the reduction reaction and the most likely way it can do this is by coordinating to palladium. The following reaction mechanism was proposed (Scheme 63).



Scheme 63. Proposed reaction mechanism for the formation of oxazines by reaction of nitroarenes and dienes.

Overall, the use of phenyl formate as a CO surrogate in the field of the reductive cyclization of nitroarenes appears to be very promising. Not only the reaction can be performed without the use of pressurized CO and specialized equipment, but yields are even higher than those obtained by the use of gaseous CO.
The optimization of other reactions is ongoing in our laboratories and the synthesis of carbazole from *o*-nitrobiphenyl has already been improved to give the product in a 72% yield.
Cesium formate has also been employed as a CO surrogate for the cyclization reaction of unsaturated nitrothioethers and nitroethers to dihydro-benzothiazines and dihydro-benzoxazines respectively.[186] The reaction needs a promoter and best results were obtained by using $SnCl_2$. Other Lewis acids gave either low yields or mixtures of products. Other formates (sodium, potassium, ammonium) or formic acid gave either low yields or mixtures of products when employed in place of cesium formate. Use of $Pd(PPh_3)_2Cl_2$ as catalyst in place of $PdCl_2$ further improved the activity of the system. The reaction tolerates both electronwithdrawing and electrondonating substituents on the nitroarene and one example of the synthesis of a tetrahydroquinoline (X = CH_2 in scheme 64) was reported.

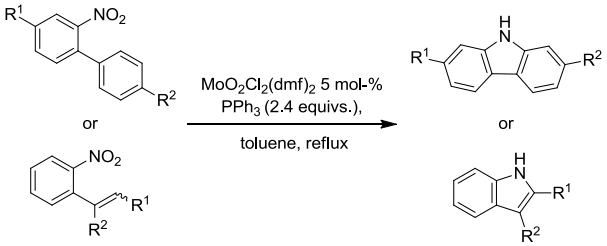


Scheme 64. Use of HCOOCs as a CO surrogate.

7. Use of molybdenum catalysts with phosphines or glycols as reductants

7.1. Synthesis of five-membered ring heterocycles using phosphines as reductants

As mentioned in the introduction, CO (either gaseous or "entrapped" in a releasing molecule) is by far the most studied reductant for the metal-catalyzed synthesis of heterocycles from nitro compounds. However, several other reductants can be used to accomplish the deoxygenative cyclization reaction even in the absence of a metal catalyst. One of the most studied class is that of alkylphosphites and especially $P(OEt)_3$. The procedure was first reported by Cadogan for the synthesis different heterocycles from nitrocompounds.[187] Although the reaction is a useful synthetic tool, it suffers from a main selectivity drawback. In fact, *N*-alkoxy and *N*-alkyl heterocycles are often formed as side products. A way to overcome this drawback was found in the use of phosphines as reducing agents instead of phosphites. In these cases, however, high reaction temperature (165-180°C) have to be kept for a long time to achieve full conversions.[188]
The use of molybdenum compounds as oxo-transfer reactants is well known due to their presence in enzymes involved in such processes.[189-190] Taking advantage of this feature of the Mo(VI)-Mo(IV) couple, Sanz reported a molybdenum catalyzed version of the PPh_3-based Cadogan reaction for the cyclization of 2-nitrobiphenyls and 2-nitrostyrenes respectively to carbazoles and indoles (Scheme 65).[191]



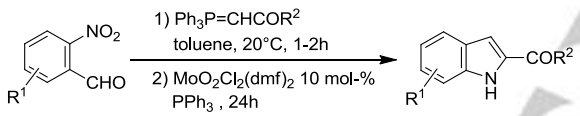
Scheme 65 Reductive cyclization of 2-nitrobyphenyls and 2-nitrostyrenes catalyzed by $MoO_2Cl_2(dmf)$ using PPh_3 as the reductant.

For this transformation, $Mo_2O_2Cl_2(dmf)_2$, which can be prepared easily and using inexpensive precursors, was advantageously used as catalyst.
A high conversion of 2-nitrobiphenyl to carbazole by PPh_3 using $Mo_2O_2Cl_2(dmf)_2$ (5 mol-%) as the catalyst was achieved in refluxing toluene in 16h. As a comparison, the uncatalyzed

reaction yielded mainly unconverted nitroarene under the same conditions. $P(OEt)_3$ was found less effective as the final reducing agent with respect to PPh_3. When applied to the synthesis of substituted carbazoles, the reaction afforded high yields with both electron withdrawing and electron donating substituents on the arene bearing the nitro group, although slightly higher amounts (>10%) of the corresponding anilines were also detected for electron rich substrates. Only moderate yields of carbazole were noticed when substituent with acidic protons (i.e. -OH, -COOH) were present. This is anyway interesting, since the uncatalyzed reaction completely failed in these cases.

The cyclization of 2-nitrostyrenes to indoles by PPh_3 can also be achieved by using the molybdenum(VI) catalysts, whereas the reaction completely failed in the absence of it. Moderate to high yields were obtained for nitrostyrenes differently substituted on the double bond. Remarkably, also polymer-bound PPh_3 could be employed in the protocol for the synthesis of both heterocyclic scaffolds without loss of selectivity, although with a decreased activity of the system.

The authors also reported the application of the same protocol to a one-pot procedure to prepare 2-acylindoles and 2-indolecarboxylates from 2-nitrobenzaldehyde. The nitrostyrenes were prepared *in-situ* by a Wittig reaction between the aldehyde and phosphonium ylide and subsequent addition of PPh_3 and the Mo catalyst allowed to achieve the cyclization (Scheme 66).



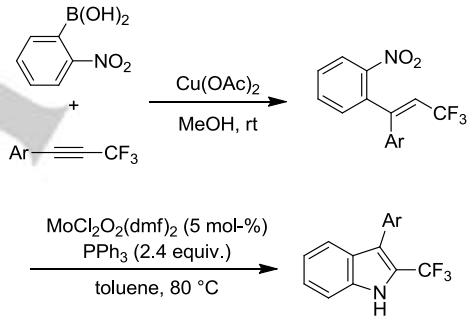
Scheme 66. One-pot synthesis of indoles from 2-nitrobenzaldehyde.

Owing to its very good group tolerance and wide applicability, the Mo(VI) catalyzed reductive cyclization took hold as a synthetic tool for the synthesis of libraries of compounds and complex molecules containing the indole scaffold. A first example is represented by the synthesis of either unsubstituted or 4,7-bromo-disubstituted 5,6-dimethoxyindoles and 5,6-dimethoxyindole-2-carboxylates.[192] The cyclization of the model substrate, methyl 3-bromo-4,5-dimethoxy-2-nitrocinnamate, afforded only complex mixtures of products when either different phosphites under "classical" Cadogan-Sundberg conditions or PPh_3 at high temperature were used. Instead, the cyclization to indole occurred selectively in 24h when $MoO_2Cl_2(dmf)_2$ was employed as a catalyst under Sanz's conditions. Notably, the reaction was complete in only 1h when performed at 200 °C under microwave irradiation. In addition, to demonstrate the tolerance of the MW procedure to different conditions, it was shown that very good to excellent yields can be obtained in less than 2h independently from the polarity of the aprotic solvent and using temperatures ranging from 120 °C to 200 °C (Scheme 67).

Scheme 67. Synthesis of 5,6-dimethoxyindoles and 5,6-dimethoxyindole-2-carboxylates.

The authors reported also the effective use of different phosphines, among which 2-(diphenylphosphino)benzoic acid is the most interesting due to its low cost and the insolubility of its phosphine oxide, which allows for an easy separation from the final products of the reaction.

The scope of the molybdenum catalyzed reaction was further extended by other groups. Yamamoto and coworkers reported the synthesis of 3-aryl-2-(trifluoromethyl)indoles by sequential copper-catalyzed hydroarylation of (trifluoromethyl)alkynes followed by reductive cyclization (Scheme 68).[193]



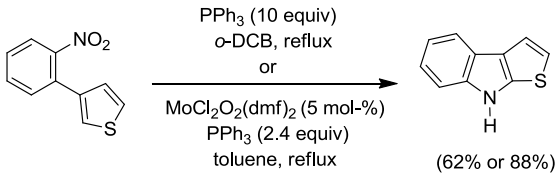
Scheme 68. Synthesis of 3-aryl-2-(trifluoromethyl)indoles.

Worth of note, the presence of the strong electronwithdrawing trifluoromethyl group, as already mentioned in section 2.8, facilitates the reduction of the nitro group. Indeed, the cyclization afforded indoles in very good to quantitative yields in only 1-3h at 80 °C, whereas usually higher temperatures and much longer reaction times were needed.

Later, the scalability and the wide applicability of the procedure reported by Sanz, was confirmed by another group by preparing a library of substituted 2-phenylindoles from 2-nitrostilbenes on a gram scale. The so prepared indoles were then tested as aromatase inhibitors.[194]

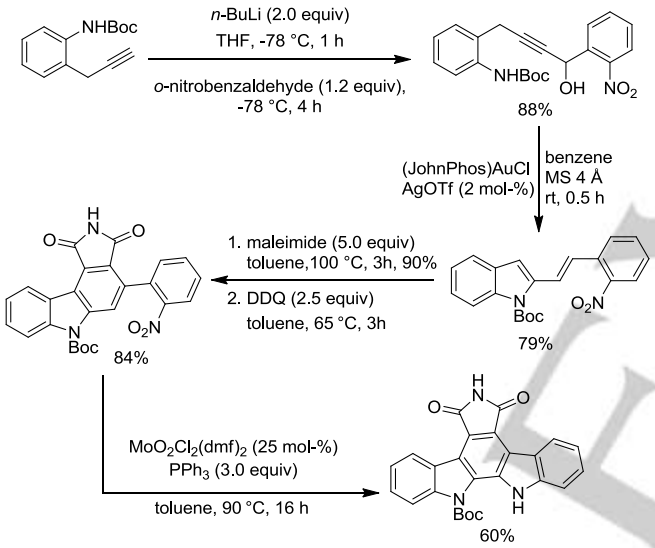
The conditions reported by Sanz for the Mo-catalyzed reductive cyclization protocol, allowed also to synthesize in very good yield 8*H*-thieno[2,3-b]indole from 3-(2-nitrophenyl)thiophene, used as scaffold for the synthesis of push-pull chromophores. Worth of note, when the reaction was performed without a catalyst, using $P(OEt)_3$ as both solvent and reductant (classic Cadogan-Sundberg conditions), side products formed to a relatively large extent. In addition, also the use of PPh_3 in the

absence of a catalyst only afforded fair yields, although with a higher selectivity with respect to the use of $P(OEt)_3$ (Scheme 69).[195]



Scheme 69. Synthesis of 8*H*-thieno[2,3-b]indole.

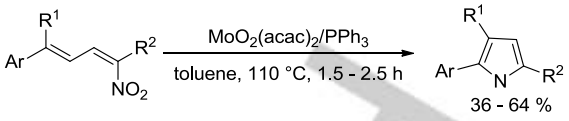
The application of the Mo-catalyzed reductive cyclization to the synthesis of complex molecules is exemplified in the preparation of the Boc-protected Arcyriaflavin A, an indolocarbazole alkaloid. The synthetic sequence is reported in scheme 70.[196]



Scheme 70. Synthesis of Boc-protected Arcyriaflavin A.

The last step in the synthesis is the reductive cyclization of a nitro substituted intermediate. The authors reported that the cyclization to get the five-membered heterocycle could not be accomplished using the uncatalyzed Cadogan reaction, Grignard reagents or different amination methods. On the other hand, $MoO_2Cl_2(dmf)_2/PPh_3$ effected the cyclization smoothly at 90°C.

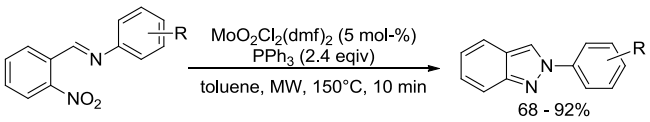
In addition to the above-mentioned specific applications of molybdenum as catalyst, Karimi and coworkers showed its use for the cyclization of conjugated nitrodienes to pyrroles using PPh_3 as the reductant (Scheme 71).[197] Few years before, it had been reported that conjugated nitrodienes can be cyclized by a "classic" Cadogan-type reaction in very good yield. However only one example had been shown.[198]



Scheme 71. Synthesis of pyrroles from nitrodienes catalyzed by dioxomolybdenum complex

Trying to extend the scope of the uncatalyzed reaction, Karimi found that only low yields could be obtained for different substrates. Moderate to good yield were instead obtained with a dioxomolybdenum(VI) catalyst in combination with PPh_3.[197] The scope of the reaction anyway must be further explored since it was tested in the presence of only few "non-challenging" functional groups. Curiously, $MoO_2(acac)_2$ was used for this transformation as catalyst instead of $MoO_2Cl_2(dmf)_2$, although a direct comparison was not present. In this regards, $MoO_2(acac)_2$ was previously reported only for the cyclization of methyl 4-(4-cyano-2-nitrostyryl)benzoate to the corresponding indole. Yet, in that case $P(OEt)_3$ was used as reductant and solvent at 130 °C, not allowing to understand if the reaction is indeed catalyzed or not.[199]

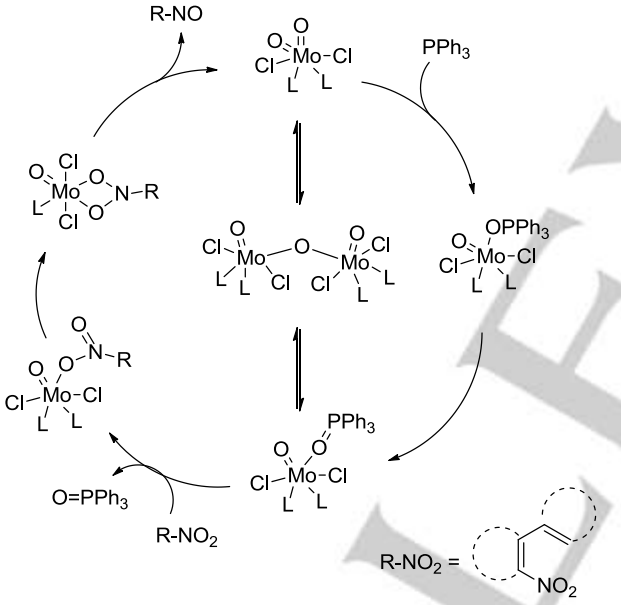
Besides the synthesis of heterocycles containing only one heteroatom, the group of Beifuss studied the application of the Mo-catalyzed cyclization using phosphines as reductants to the synthesis of azoles and azines. In particular, the cyclization of 2-nitrobenzylidene amines using PPh_3 as reductant afforded 2-aryl-2*H*-indazoles in good to excellent yields. Only 10 minutes at 150 °C under MW heating in toluene were required to reach complete conversion of the nitroarene (Scheme 72).[200] The transformation occurred smoothly also under thermal heating either at 150 °C or at reflux in toluene, albeit with diminished yield and 30-fold longer reaction times. Only a little effect of the substituent on the *N*-aryl ring of the imine was noticed. This is not surprising since it has a negligible influence on the nitroarene reduction to nitroso, which is expected to be the rate determining step.



Scheme 72. Synthesis of 2-aryl-2*H*-indazoles.

Concerning the mechanism of the $MoO_2Cl_2(dmf)_2$ reductive cyclizations described above, based on their previous studies on deoxygenation of sulfoxides with phosphites, Sanz and coworkers proposed that the catalytic cycle starts with an oxygen atom transfer from the dioxomolybdenum(VI) to the final reductant (*i.e* phosphine or phosphite).[201] It is generally accepted that deoxygenation of Mo(VI) oxo-complexes takes place through a nucleophilic attack of the phosphine on a $\pi^*_{Mo\text{-}O}$ orbital, leading to the formation of a Mo(IV) complex and $O{=}PR_3$.[202-203] The formed $Mo^{IV}OCl_2L_2$, where L could be either dmf, phosphine, phosphinoxide, readily comproportionate with

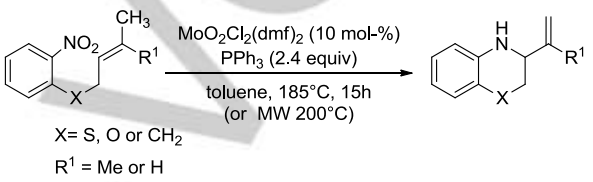
the unreacted $Mo^{VI}O_2Cl_2L_2$ to yield $Mo_2{}^{V}O_3Cl_4L_4$, the dimeric species being in equilibrium with the two monomers.[191, 204] This kind of dimeric species are generally more difficult to be reduced, being thus less active or inactive in the catalytic cycle.[189] Subsequently, the reduction of the nitro group is proposed to occur by initial coordination of one oxygen atom of the nitro group to the molybdenum. A more stable chelate is next formed in which the nitro group coordinates with both oxygen atoms. Then, the oxygen atom is transferred to molybdenum as a consequence of the *N*-O bond cleavage, leading to a coordinated nitroso compound (Scheme 73). Theoretical calculations performed on MoO_2Cl_2 identified this pathway as the most favored.[205] The nitrosoarene formed after the first deoxygenation can be further deoxygenated to form an imido complex or leave the coordination sphere of molybdenum. Although there is no evidence for one or the other pathway, it is generally proposed that the second deoxygenation/cyclization steps take place off-metal.[191, 205] The assumption is mainly based on the observation by Cadogan that reductive cyclization of *o*-nitrosobiphenyl with either triethylphosphite or triethylphosphine readily takes place in benzene at 0 – 5 °C.



Scheme 73. Mechanistic proposal for the Mo-catalyzed deoxygenation of nitro compounds to nitroso intermediates by PPh_3.

7.2. Synthesis of six-membered ring heterocycles using phosphines as reductants

Following the first report by Sanz, the group of Beifuss studied the application of dioxomolybenum complexes as catalyst for the synthesis of six-membered ring heterocycles (Scheme 74).[206] Initially, $P(OEt)_3$ and PPh_3 were compared in the absence of any catalyst for the cyclization of 2-allyl-nitrophenyl thioethers to 3,4-dihydro-2*H*-1,4-benzothiazines. As previously noted, when the phosphite is used both as a solvent and a deoxygenating agent, *N*-ethylated heterocycles formed. This side reaction is suppressed if the reaction was performed under MW irradiation in toluene, however, a large excess of $P(OEt)_3$ (6 equiv.) was necessary. On the other hand, the use of PPh_3 allowed to use an almost stoichiometric amount of reductant both in the presence and in the absence of a catalyst and both under thermal (185 °C in a sealed vessel) and MW (200 °C) heating. The authors showed that in the absence of catalyst the benzothiazine yield was only moderate and it could be improved by using amounts of $MoO_2Cl_2(dmf)_2$ comprised between 5 and 10 mol-% under thermal conditions. The reaction time was reduced from 10-15 h to half an hour when MW heating was used. In addition, the cyclization could be performed in several polar and not-polar aprotic solvents without significant drops in yield

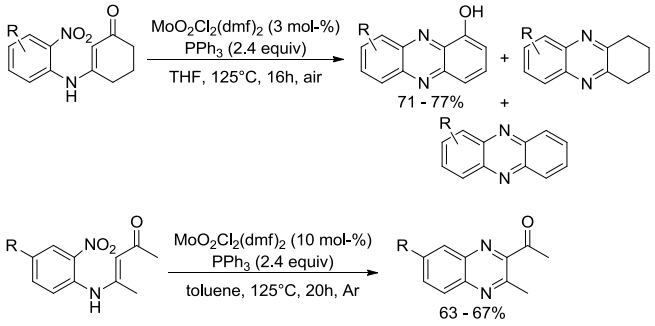


Scheme 74. Synthesis of 3,4-dihydro-2*H*-1,4-benzothiazines, 4-dihydro-2*H*-1,4-oxazines and 1,2,3,4-tetrahydroquinoline.

The protocol was extended to the synthesis of 4-dihydro-2*H*-1,4-oxazines and 1,2,3,4-tetrahydroquinoline by the cyclization of the corresponding nitroalkenes.

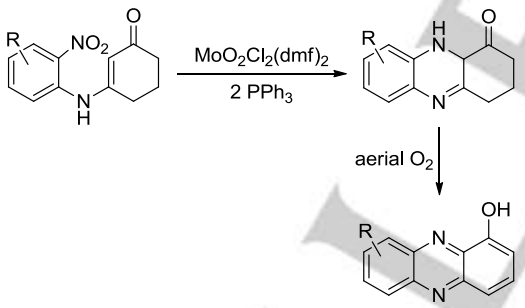
From a mechanistic point of view, the general reaction pathway does not differ from the one described for five-membered ring heterocycles (Scheme 73). However, it should be mentioned that for 2-allyl-nitrophenyl thioethers no reaction occurs when the olefinic bond is unsubstituted (R^1 = H and the methyl group is replaced by H in scheme 74). This result indicates that the reductive cyclization occurs through a nitroso-ene reaction mechanism, thus supporting the hypothesis of a nitrosoarene intermediate. Indeed, if a nitrene intermediate were involved, the reaction should proceed even in the absence of a methyl substituent on the olefin.

In addition to the above-mentioned heterocycles, the synthesis of 1-hydroxyphenazines from cyclic β-(*N*-2-nitroaryl)-α,β-unsaturated ketones using PPh_3 as reductant was also reported (Scheme 75).[207] The only previous preparation of 1-hydroxyphenazine by reductive annulation of a nitroarene was described by Söderberg, albeit only a low yield (26%) had been obtained.[86]



Scheme 75. Mo-catalyzed synthesis of 1-hydroxyphenazine and quinoxalinyl ketones.

Indeed, the reaction is more difficult to achieve with respect to the other cyclizations discussed in this section since it involves an initial reductive cyclization step followed by two oxidative dehydrogenation steps. Malakar and co-workers were able to obtain good yields of 1-hydroxyphenazines using the $MoO_2Cl_2(dmf)_2/PPh_3$ system (3 mol-%/2.4 equiv) in THF at 125 °C for 16h under air. Different substituents in *meta* position with respect to the nitro group were well tolerated, but only traces of product were formed when either a chloride in the *para* position or a methyl or phenyl group in the position 3 of the cyclohexanone ring was present. The cyclization of acyclic β-(*N*-2-nitroaryl)-α,β-unsaturated ketones to quinoxalinyl ketones was also achieved, although a higher catalyst loading and longer reaction times were required to get satisfactory yields (Scheme 76).

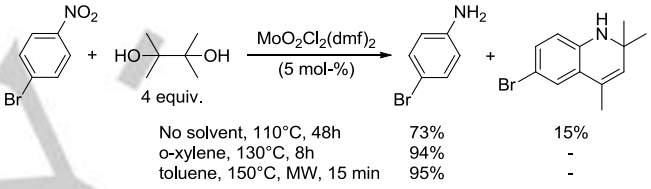


Scheme 76. Proposed mechanistic pathways for the formation of 1-hydroxyphenazines.

The authors propose that aerial oxygen is responsible for the oxidative dehydrogenations and the reaction is possibly catalyzed by Mo(VI). Unfortunately, the role of molybdenum in the oxidation process is not clear

7.3. Synthesis heterocycles using glycols as reductants

The molybdenum-catalyzed reductive cyclization reactions described above allow the synthesis of different heterocyclic compounds without the need for gaseous CO. However, the required stoichiometric amounts of phosphines used as the reductant constitute a major drawback for large scale reactions. In fact, the production of two equivalent of phosphine oxide as side product limits the applicability of the protocol. To overcome the problem, Sanz and coworkers first employed pinacol as the reductant for deoxygenation reactions catalyzed by dioxomolybdenum complexes.[208] Apart from the higher sustainability of pinacol as reagent with respect to P-based reductants, the main advantage of the use of this diol in addition to its low cost is clearly the easy elimination of its excess and of the formed byproducts (acetone and water) from the final product. The reduction employing pinacol was first optimized on the deoxygenation of sulfoxides to thioethers. The optimal settings found for this reaction were then used as the starting point for the reduction of nitroarenes. The reaction conditions required for the reduction of the nitro group were a bit harsher than those required for sulfoxides, albeit still relatively mild (4 equiv. pinacol, 110-130 °C using 5 mol-% of catalyst, Scheme 77).



Scheme 77. Mo-catalyzed reduction of nitroaromatics using pinacol as deoxygenating agent.

Under optimized conditions, the selective reduction of a wide range of substituted nitroarenes was achieved. Among these, also 2-nitrobiphenyl was reduced to 2-aminobiphenyl selectively. This result indicates that the hydrogenation of the intermediately formed 2-nitrosobiphenyl is faster than the cyclization to carbazole.

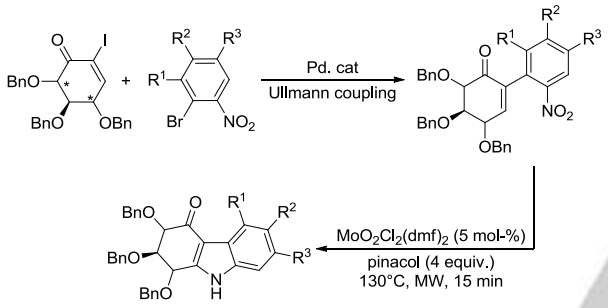
When pinacol was used as both as the solvent and the reducing agent, dihydroquinoline was obtained as side product (Scheme 77). This originates from the condensation of the formed aniline with two equivalents of acetone derived from pinacol oxidation. This tandem reaction was then further developed by Sanz using different glycols in order to obtain more complex heterocycles.[209]

Although the reduction of 2-nitrobiphenyl did not afford carbazole, later reports demonstrated that pinacol is a suitable reductant for the reductive cyclization of substrates bearing in the *ortho* position with respect to the nitro group a substituent having a C=C double bond. In these reactions, the amination of the double bond by an intermediately formed nitrosoarene is faster than the competing reduction to amine.

Thus, following the work by Sanz, Malakar and Beifuss studied the application of pinacol as deoxygenating agent for the molybdenum catalyzed synthesis of six-membered ring heterocycles.[210] 1,4-Benzoxazines, 1,4-benzothiazines, 1-hydroxyphenazines and quinoxalinyl ketones were obtained in good to very good yields at 110 °C in 10h using 2.5 mol-% of

$MoO_2Cl_2(dmf)_2$ and 5 equiv. of pinacol. Although a number of solvents can be employed, the use of neat pinacol ensured the best yields, differently from what was found for the reduction of nitroarenes to anilines. Interestingly, also the complex MoO_2Cl_2 was effective as catalyst for the transformation, although with a diminished yield.

The synthesis of chirally enriched tetrahydrocarbazolones is the last application of pinacol to a reductive cyclization of nitrostyrenes reported so far.[211] Taking advantage of the natural chirality of D-glucose, D-galactose and D-mannose, Sagar and coworkers prepared three α-iodo cyclohexenones and coupled them by palladium catalyzed Ullmann reaction with several substituted *o*-bromo nitroarenes. The obtained nitrostyrenes were then cyclized to the corresponding tetrahydrocarbazolones using 5 mol-% $MoO_2Cl_2(dmf)_2$ as catalyst and either PPh_3 or pinacol as the reductants (Scheme 78).

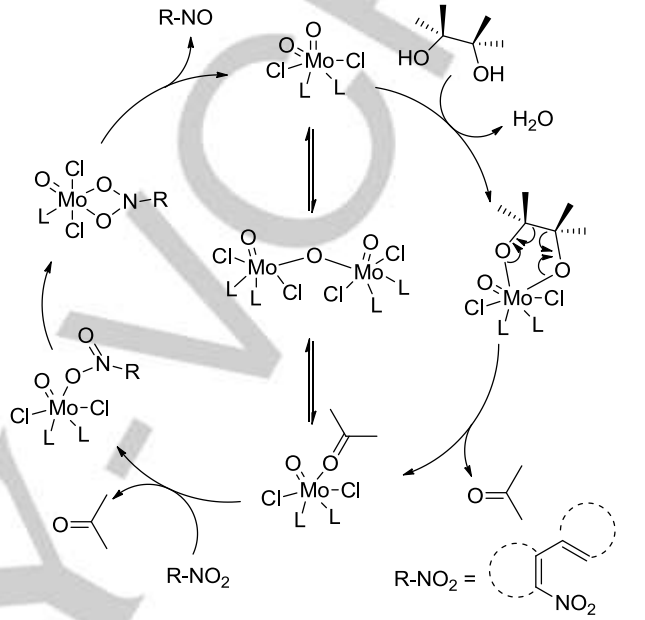


Scheme 78. Synthesis of chirally enriched tetrahydrocarbazolones.

Under microwave heating at 130 °C, the reaction afforded the product in only 15 minutes. Slightly higher yield (70 %) were obtained when pinacol was used rather than PPh_3 (60%). The cyclization could be also efficiently achieved under thermal heating, although after a much longer reaction time (12h). Although both reductants are efficient, as already mentioned before, the use of pinacol allow a faster and easier purification of the product, which is particularly important in the case of highly substituted compounds. Electron withdrawing and electron releasing group were well tolerated. A low yield was obtained when a second nitro group was present on the aromatic ring, most likely due to its partial reduction.

From a mechanistic point of view, the molybdenum catalyzed deoxygenation of different substrates only differs from the PPh_3 based system for the initial reduction of the Mo(VI) complex by pinacol.

Sanz proposed for the reduction of sulfoxide that the catalytic cycle starts with the condensation of $MoO_2Cl_2L_2$ with pinacol affording the complex MoO(pinacolate)Cl_2L_2 and water. Then oxidative cleavage of the diol affords $MoOCl_2L_2(Me_2CO)$ and acetone. The weakly coordinated acetone is readily replaced by a molecule of the substrate.[208] In the case of nitroarenes the nitro group is then deoxygenated yielding a nitroso compound as discussed for the analogous reaction using phosphines as reductants. Differently from the phosphine-based reduction, the further deoxygenation of nitrosoarene cannot be performed in the absence of the metal catalyst. Although to date there is no evidence to exclude a metal mediated cyclization, by analogy to previous discussed systems, it is most likely that the nitroso intermediate acts as the aminating species forming an *N*-hydroxyheterocyclic intermediate, which is then deoxygenated by a $MoOCl_2L_2$ complex (Scheme 79).

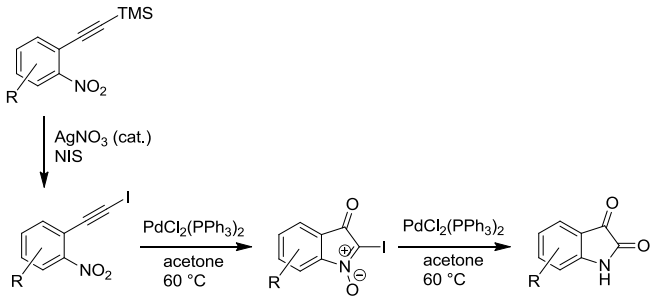


Scheme 79. Mechanistic proposal for the Mo-catalyzed deoxygenation of nitro compounds to nitroso intermediates by pinacol.

8. Miscellaneous reactions

Only a few cyclization reactions relevant to this review do not follow in any of the classes described in the previous paragraphs and are described here. In most cases, only one paper has been published employing a certain strategy, but some results appear to be very interesting and are surely amenable to an extension to other cyclization reactions. Thus, these may just be the first examples of what will become different classes of reactions in the future.

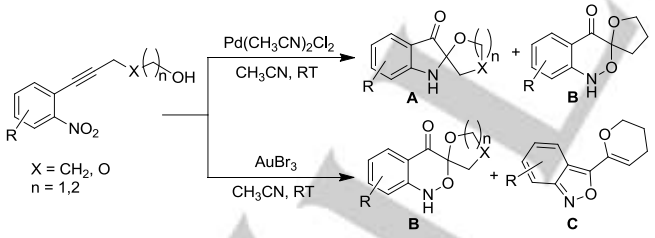
While attempting to expand the range of substrates that can be cyclized in a palladium catalyzed reaction, Söderberg found that several palladium(II) complexes catalyze the cyclization of *o*-(haloethynyl)nitroarenes to the corresponding 1*H*-indole-2,3-diones (isatins) (Scheme 80).[212]



Scheme 80 Synthesis of isatins (NIS = *N*-iodosuccinimide).

The reaction was at first performed under a CO pressure, but it turned out that CO not only is not required for the reaction to proceed, but even has a negative influence on its outcome. Indeed, the reaction appears to be catalyzed by a palladium(II) compound and use of a palladium(0) precursor led to an intractable mixture of products. Best conditions were found to involve the use of the iodo derivative as substrate and $PdCl_2(PPh_3)_2$ as catalyst, in acetone as solvent and at 60 °C in a closed pressure vessel. The chloro and bromo derivatives could also be employed, but yields were lower. Both electronwithdrawing and electrondonating substituents on the nitroarene can be present and steric hindrance is also tolerated, but the reaction failed if the nitro group was on a pyridinic ring. Characterization of an intermediate in the reaction allowed to conclude that the reaction proceed through the formation of 2-halo-isatogens (Scheme 80). The starting materials for the reaction are not stable molecules and were prepared from the corresponding trimethylsilyl derivatives by reaction with $AgNO_3$ and *N*-iodosuccinimide immediately before the catalytic reaction was performed.

o-Nitroalkynyl derivatives of a different type are also the starting materials in a work by Patel and Ramana (Scheme 81).[213]



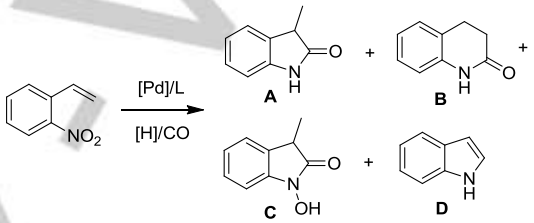
Scheme 81. Nitroalkynol cycloisomerization reactions.

The reaction yielded different products when catalyzed by palladium or gold salts or complexes. The highest selectivities were achieved by using either $Pd(CH_3CN)_2Cl_2$ or $AuBr_3$ as catalysts. In the former case, the main product was indolinone **A** in Scheme 81, which however was formed in a *ca.* 1:1 mixture with the benzoxazinone **B** when X = CH_2 and n = 1 in the scheme. On the other hand, the gold catalyzed reaction gave a complex mixture of products when X = CH_2 and n = 1, but selectively gave compound **B** for X = O and n = 2. However, if X = CH_2 and n = 2, a *ca.* 1:1 mixture of **B** and **C** was obtained.

The reaction is likely to start with the formation of a η^2-complex between the metal and the triple bond, followed by an intramolecular attack of an oxygen atom of the nitro group on the *alpha* (for palladium) or on the *beta* (for gold) carbon atom on the alkyne. However, the following steps are less clearly identifiable in a clear-cut way.

It should be noted that formation of compound **A** requires a reduction to occur at some stage. The fate of the lost oxygen atom was not discussed. The only compound present in solution that may be oxidized appears to be the substrate itself.

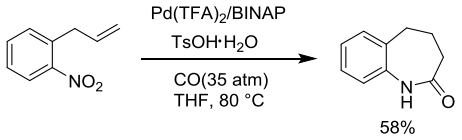
We have mentioned in paragraph 2 that the presence of water or protic sources is generally to be avoided if cyclization reactions of the kind investigated here are to be performed. Li and coworkers did instead added protic sources intentionally to get different products (Scheme 82).[214]



Scheme 82. Synthesis of carbonylated products.

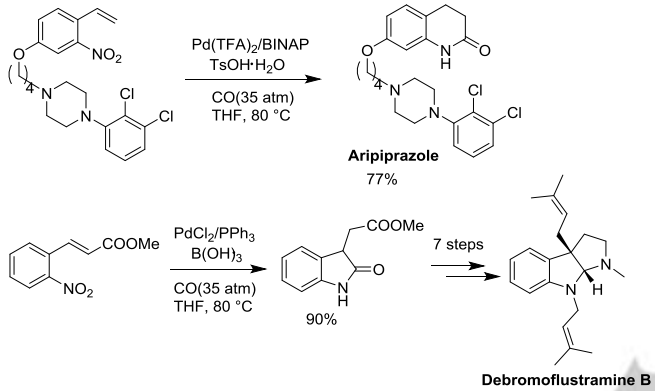
An extensive screenings of palladium salts, ligands and hydrogen sources was performed to maximize the yield of either indolone **A** or quinolinone **B**, minimizing their cross contamination and the formation of other byproducts, among which *N*-hydroxyindolone and indole were clearly identified and quantified. The results were very sensitive to apparently minor variations in the catalyst. For example, with triphenylphosphine as a ligand and boric acid as the hydrogen source, $PdCl_2$ and $Pd(TFA)_2$ gave mostly compound **A,** whereas $PdBr_2$ and $Pd(OAc)_2$ led to preferential formation of indole **D**. Overall, the best conditions to obtain indolinone **A** were the use of $PdCl_2$ (5 mol-%) in the presence of PPh_3 (10 mol-%) and $B(OH)_3$ (2 equiv.), under CO (35 atm), in THF at 80 °C. On the other hand, for dihydroquinolinone **B** were the use of $Pd(TFA)_2$ (5 mol-%) in the presence of BINAP (5 mol-%) and $TsOH•H_2O$ (2 equiv.), under CO (35 atm), in THF at 80 °C.

Substitution of the terminal carbon atom of the styrene had little effect on the production of indolinones, but almost completely prevented the formation of dihydroquinolinones. A similar effect of steric hindrance was found when the effect of a substituent in the *ortho* position of the aryl ring of the nitroarene was investigated. Here also, the effect was small in the formation of **A** and large for the formation of **B**. Interestingly, the reaction could be extended to a nitroarene bearing an allyl, instead of a vinyl, group, affording a seven-membered benzazepinone (Scheme 83). This extension is not usually possible for most of the reactions here described.



Scheme 83. Synthesis of benzazepinone.

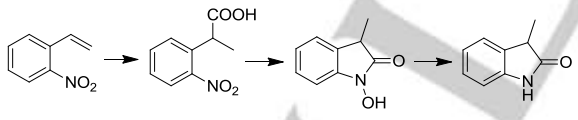
The optimized conditions were also successfully applied to the synthesis of a pharmaceutically important drug (aripiprazole, Abilify) and of an intermediate in the synthesis of another one (Debromoflustramine B)(Scheme 84).



Scheme 84. Synthesis of aripiprazole and debromoflustramine.

Several experiments were performed to elucidate the reaction mechanism.

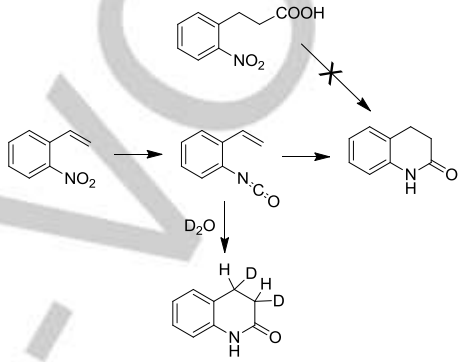
The synthesis of indolones was clearly shown to proceed by a hydroxycarbonylation of the vinyl group to give an arylpropanoic acid, whose further reduction affords an *N*-hydroxyindolinone, which is finally deoxygenated by CO to give the final product (Scheme 85). The presence of CO was found to be necessary for all the steps reported.



Scheme 85. Sequence of organic intermediates in the synthesis of indolinones.

The cyclization was proposed to occur after the nitro group has been reduced to nitroso. However, nitrosoarenes are weak nucleophiles and we are not aware of any reaction between nitrosoarenes and carboxylic acids to give acylhydroxylamines (an oxygen atom should be liberated). In our opinion, it is more likely that reduction of the nitro group proceeds up to the hydroxylamine stage, a process favored by the presence of a proton source, and that it is the hydroxylamino group that attacks the carboxylic one, with liberation of water.

A different mechanism surely operates when quinolinones are formed. Indeed, reaction of *o*-nitrophenylpropionic acid under the standard catalytic conditions for the synthesis of quinolones failed to give any of the latter product. On the other hand, independently synthesized *o*-vinyl-phenyl isocyanate did afford the quinolinone in excellent yields. Moreover, when D_2O was employed as the hydrogen source, the deuterium incorporation was almost indistinguishable for the quinolinone obtained starting from *o*-nitrostyrene and that obtained by using *o*-vinyl-phenyl isocyanate as the starting material (Scheme 86).

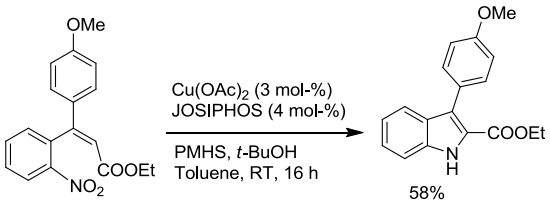


Scheme 86. Sequence of intermediates in the synthesis of quinolinones.

Thus, it appears that in this case the carbonylation reaction occurs on the side of the nitro group and not on the alkene side.

Silanes and disilanes has long been known to promote the reduction of nitroarenes even in the absence of a metal catalyst and the reaction can be employed for the synthesis of heterocyclic compounds,[215-217] but high temperatures are needed unless activated silanes are employed.[217] Iron complexes have been found to catalyze the reduction of nitroarenes to anilines by phenylsilane.[218]

A single example of the use of a copper catalyst in the reductive cyclization of a nitrostyrene to indole by a silane was reported in 2011 by Taylor and Correia (Scheme 87).[219]

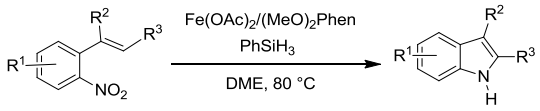


Scheme 87. Copper catalyzed reductive cyclization of a nitrostyrene to indole using PMHS as reductant.

The reaction was serendipitously discovered while investigating a different class of reactions and only one example was provided. However, the reaction would be very interesting if it can be applied even to other substrates because it occurs at room temperature with an inexpensive copper catalyst. The reductant, polymethylhydrosiloxane (PMHS) is a byproduct of

the silicone industry and is cheap with respect to other silanes. A chiral phosphine was employed, but this is clearly not necessary for this reaction. A 58% yield was obtained, but no optimization of the reaction conditions was performed, so that yields may likely be increased.

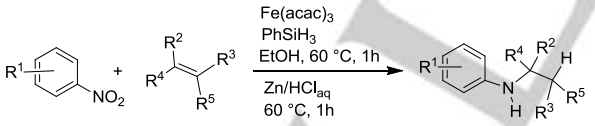
Driver also employed silanes to effect the same kind of cyclization reaction.[88] An extensive screening of catalysts was performed. Best results were obtained by using $Fe(OAc)_2$ as catalyst, $(MeO)_2$Phen as ligand, and phenylsilane as the reducing agent, in DME as solvent at 80 °C (Scheme 88).



Scheme 88. Iron catalyzed reductive cyclization of nitrostyrenes to indoles using $PhSiH_3$ as reductant.

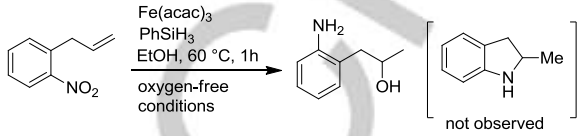
Excellent yields were obtained in many cases and the reaction tolerates both electrondonating and electronwithdrawing substituents on the aryl ring. Steric hindrance is also tolerated both on the aryl ring and the vinyl moiety. However, the reaction could not be extended to the cyclization of *o*-aryl nitroarenes to carbazoles. Use of PMHS also gave much reduced yields under the same experimental conditions. *N*-Hydroxyindoles were observed in many cases, which could be reduced to indoles by the same catalytic system. Thus, it appears that even in this case the cyclization is occurring at the nitrosoarene stage. The kinetic was found to be first order in catalyst and silane, but zero order in nitroarene, implying that reduction of the iron catalyst at the end of each cycle is the rate-determining step or the reaction and activation of the nitroarene and all other steps of the reaction are comparatively faster.

It should be mentioned that the use of $PhSiH_3$ in combination with an iron catalyst had been earlier employed by Baran to effect the amination of a wide variety of alkenes by nitroarenes (Scheme 89).[220]



Scheme 89. Iron catalyzed reductive amination of alkenes by nitroarenes using $PhSiH_3$ as reductant.

The reaction requires an additional reductant (Zn/HCl) to be completed and appears to be mechanistically different from the allylic amination reactions discussed previously in paragraph 5.1. Indeed, in the latter case, the amination reaction was accompanied by a double bond transposition and the C-N bond was formed at the terminal position of the olefinic bond when possible. On the other hand, with the Baran system the C-N bond is formed at the most substituted position of the alkene. It appears that the reaction proceeds by reduction of the alkene to give an alkyl radical, which attacks a nitrosoarene independently formed by reduction of the nitroarene. The reaction is extremely versatile and although the only substrate that may have yielded a heterocyclic system failed to do so (Scheme 90), room surely exists to extend this kind of reactivity to the synthesis of heterocycles and the system developed by Driver may just be the first example of this kind.



Scheme 90. Iron catalyzed reduction of allylnitrobenzene using $PhSiH_3$ as reductant.

Finally, we want to mention that selenium is also a catalyst for several reductive cyclization reactions of nitroarenes by CO. Since selenium is not a transition metal, these reactions have not been included in this review, but the older examples are cited in our previous reviews, that were focused on the use of CO.[1-2] A few papers have been published in more recent years, which had not been included in those reviews.[221-224]

9. Conclusions

The transition metal catalyzed synthesis of heterocycles by reductive cyclization of nitroarenes has been for many years the realm of carbon monoxide as the reductant. However, despite many notable achievements and a continuous development of new reactions, this synthetic strategy has not become of widespread use in synthetic laboratories surely because of the requirement for pressurized CO and partly even for the sometimes lengthy preparations of the substrates. The latter problem has been partly solved in the last decade by the development of several *inter*-molecular reactions and the use of more easily accessible nitroalkenes as starting materials. However, the most promising development in the field is the very recent use of CO surrogates, which allows the reactions to be performed even without a source of pressurized CO and the availability of autoclaves. The results already published clearly show that the use of a CO surrogate does not lead to reduced yields and more of the previously reported reactions will probably soon be performed by this way. The use of phosphines as reductants, with molybdenum catalysts, is also spreading quickly, after having been dormant for a few years after the first report. Finally, the use of glycols and silanes as alternative reductants is still in its infancy, but very promising. It is likely that the next few years will see a flourishing of new reports on their use.

Acknowledgements

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Keywords: nitroarenes • *N*-heterocycles • homogeneous catalysis • carbon monoxide • CO surrogates

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