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The reductive cyclization of *o*-Nitrobiphenyls and *o*-Nitrostyrenes to *N*-Heterocycles by carbon monoxide, catalyzed by Palladium/Phenanthroline Complexes: an experimental and theoretical mechanistic study

Manar Ahmed Fouad [a,b], Doaa R. Ramadan [a,b], Francesco Ferretti [a], Artur Brotons Rufes [c], Simona Russo [c], Piero Macchi [d], Chiara Costabile [c,*], Fabio Ragaini [a,*]

[a] Dipartimento di Chimica, Università di Milano, V. C. Golgi 19, 20133 Milano, Italy
[b] Chemistry Department, Faculty of Science, Alexandria University, P.O. Box 426, Alexandria 21321, Egypt
[c] Dipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, V. Giovanni Paolo II, Fisciano SA, Italy
[d] Dipartimento di Chimica, Materiali e Ingegneria Chimica, Politecnico di Milano, V. Bassini 6, 20133, Milano, Italy

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ABSTRACT

Competitive and trapping experiments demonstrated that the reductive cyclization of *o*-nitrobiphenyl to carbazole using CO as the reductant and a palladium/phenanthroline catalyst proceeds through the formation of free *o*-nitrosobiphenyl. A kinetic study of its cyclization reaction to *N*-hydroxycarbazole indicated that the reaction does not require a metal catalyst, but is accelerated by bases, as also observed in the catalytic reaction starting from the nitro compound. Theoretical calculations provided details on the mechanism, including the involvement of DMF (solvent), when no additional base is added. The cyclization reaction is similar in the case of the synthesis of indoles from *o*-nitrostyrenes, but the two reactions show different sensitivities to air. This was attributed to different rate-determining steps, involving a Pd(II) complex as the resting state for the synthesis of carbazoles and a Pd(0) one for that of indoles. A palladacyclic complex was isolated from a reaction of *o*-nitrobiphenyl under conditions close to those employed in the catalytic reaction and shown to afford carbazole when reacted with pressurized CO. For the synthesis of indoles, a Pd(0) olefin complex, Pd(Phen)(η^2-(*E*)-3-(5-fluoro-2-nitrophenyl)-1-phenylprop-2-en-1-one), was isolated directly from a catalytic reaction and characterized by single crystal XRD. An analogous complex, Pd(Phen)(η^2-methyl (*E*)-2-nitrocinnamate), was also independently synthesized and structurally characterized, affording 2-carboxymethyl-indole when treated with CO. Some previously reported pieces of evidence apparently in favor of the involvement of metal-imido species as intermediates in cyclization reactions of nitroarenes when CO is employed as a reductant were dismissed. In particular, a compound previously identified as an aziridine was proven to be an allylic amine, whose formation does not require a metal-imido intermediate. Overall, the results strongly indicate that the cyclization occurs outside the metal coordination sphere at the nitrosoarene stage, excluding the involvement of imido (nitrene) complexes.

1. Introduction

The transition metal-catalyzed reductive cyclization of *o*-substituted nitroarenes by carbon monoxide to give different *N*-heterocycles has been known for several decades [1] and has been the object of many reviews [2–11]. A few examples in which intermolecular reactions of a nitroarene with an alkene [12–15], diene [13,16], or alkyne [17–19] as well as reactions involving the cyclization of β-nitrostyrenes and related compounds [20–23] have also been reported (Scheme 1).

With respect to other reducing agents, CO has the advantage of producing only CO_2 as a stoichiometric byproduct, making the workup very easy. Recently, the use of CO surrogates has also been developed for several of these cyclization reactions [5,24–29], making this kind of chemistry employable even in laboratories where autoclaves and

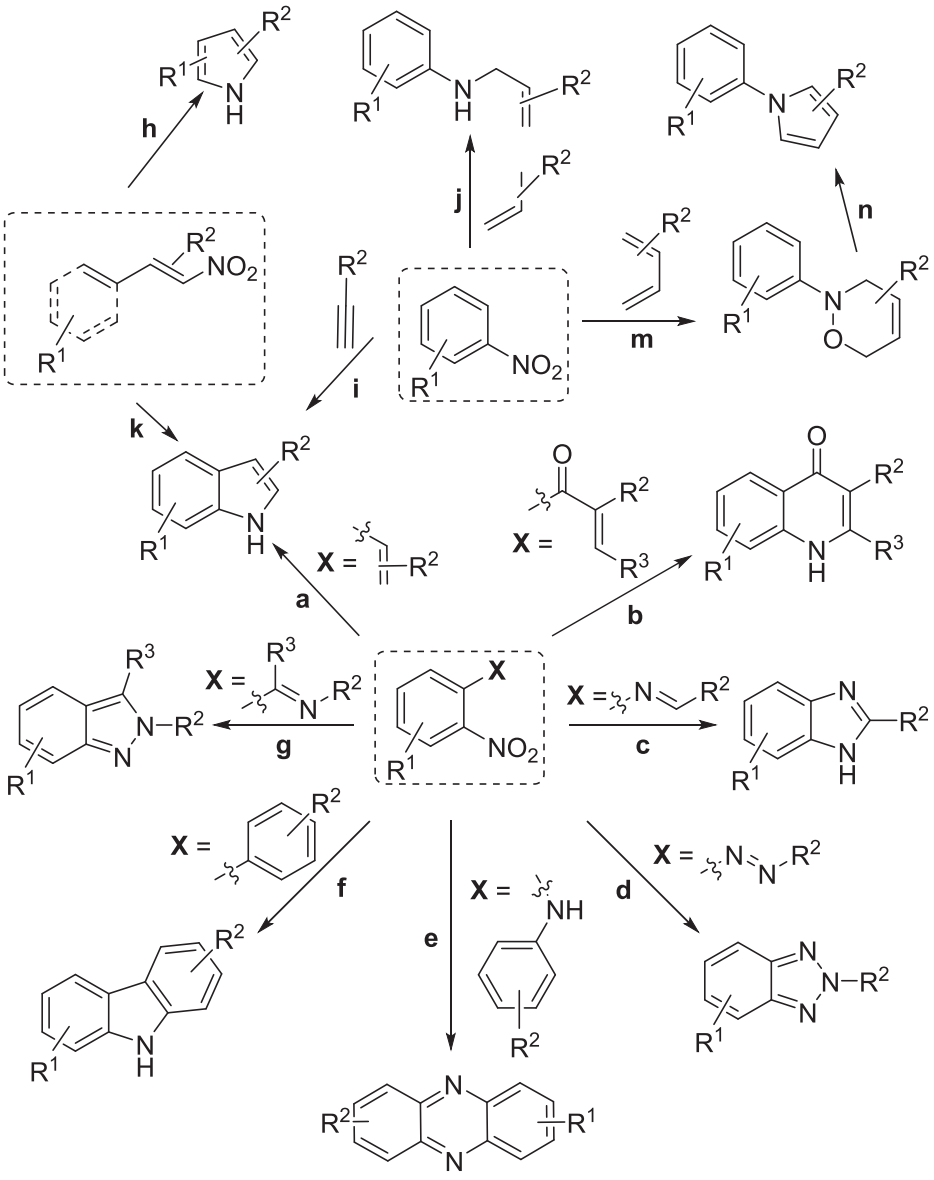
* Corresponding authors.
E-mail addresses: ccostabile@unisa.it (C. Costabile), fabio.ragaini@unimi.it (F. Ragaini).

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pressurized CO lines are not available. In particular, we have focused our interest on the use of phenyl formate or formic acid/acetic anhydride as CO surrogates for these reactions because they minimize the amount of stoichiometric byproducts, phenol or acetic acid, apart from CO_2, that are formed during the reaction [30–40]. The use of palladium/phenanthroline based catalytic systems, originally developed for the carbonylation reaction of nitroarenes to carbamates [41], was first introduced for the nitroarene cyclization reactions by Cenini and coworkers [42] and is now the most widely employed to this aim, so most of the previously cited literature makes use of it [43–46].

It should be noted that the efficacy of 1,10-phenanthroline (Phen) and related ligands in reduction by CO and carbonylation reactions of nitroarenes is due to their ability: a) to stabilize both palladium(II) and palladium(0) intermediates and b) to be inert to oxidation by the nitroarenes themselves. Phosphines can obviously fulfill the first requirement and have indeed been successfully employed as ligands for palladium in this chemistry [6,7,9]. However, phosphines directly react with nitroarenes to give phosphine oxides at high temperatures and have long been employed to this aim in Cadogan-Sundberg reactions [9]. Coordination to palladium does not prevent this reaction at the temperatures typically employed [47]. As a consequence, turnover numbers (TON) of 1000 or even higher could be reached in some reductive cyclization reactions of nitroarenes when Phen was employed as a ligand [31,38,48] and a TON as high as 10^5 when a Pd/Phen catalyst was employed in the carbonylation of nitrobenzene to methyl phenylcarbamate [49]. However, much lower TONs, typically in the range 10 to 20, are achieved when only phosphines are employed as ligands. Moreover, whenever a possible industrial application is foreseen, oxidation of the ligand would not be acceptable, both because of the cost of the phosphine and because separation of the products from phosphine oxides by crystallization has been shown to lead to unacceptable losses [48,50].

Compared with many synthetic studies dedicated to reductive cyclization reactions of nitroarenes with CO as the reductant, only scattered mechanistic tests and few theoretical calculations have been performed. These will be discussed in the text of this paper when relevant to the point examined. This work aims at drawing some conclusions, as general as possible, on some aspects of the reaction mechanism of the reductive cyclization reactions mentioned above. In doing so, we also critically re-evaluated data previously reported in the literature and, when an inconsistency was noted, we even repeated the corresponding experiment. The final scenario is consistent not only with the



Scheme 1. Selected examples of reported cyclization reactions of nitroarenes employing CO as the reductant.

newly obtained results, but also with all other results reported in the literature that are relevant to the reaction mechanisms investigated here. Given the close parallelism that exists between the key steps in different heterocyclization reactions of nitroarenes, the discussion is organized according to the elementary steps rather than to the final product, although the evident differences between the different reactions are obviously considered and discussed. The key results are that the C-N bond forming step proceeds through an off-metal reaction of an intermediately formed nitrosoarene, with dismissal of the presumed evidence in favor of the involvement of imido complexes at this stage, and the identification of the resting state of the catalytic system in two different reactions. To the best of our knowledge, the latter point has never been previously investigated in the literature. Theoretical studies were performed to support the experimental results, based on a variety of techniques, from kinetic studies to single crystal X-ray diffraction of relevant reaction intermediates.

Note that several nitroarene reductive cyclization reactions can be performed also employing other reductants apart from CO. The use of phosphites and phosphines even in the absence of any metal catalyst (Cadogan-Sundberg reactions) has long been known [51] and has even been mechanistically investigated [52,53]. The reaction with phosphines can be accelerated by the presence of a molybdenum catalyst [54,55]. Other reductants that have been employed include silanes [56,57], diols [58], and boron compounds [59]. Discussing the reaction mechanism when these reductants are employed is outside the scope of the present paper, but some results we obtained may be relevant even for the reactions carried out in their presence.

2. Results and discussion

2.1. The initial nitroarene activation

In the systems investigated so far, the reduction of nitroarenes by transition-metal complexes has been shown to proceed through an initial single-electron transfer step from the metal to the $–NO_2$ group, including nickel [60], ruthenium [61,62], iron [63–66], and rhodium [67–69] complexes. In case of palladium, a direct evidence for the formation of a nitroarene radical anion has only been gained recently for a specific nitroarene, namely nitro-perylenediimide [70], but indirect evidence for such an event in the case of palladium/Phen catalytic systems and *o*-nitrostyrenes can be gained from kinetic measurements. When differently substituted *o*-nitrostilbenes were reacted in competition with the unsubstituted substrate, a linear correlation was found between the log k_{rel} and the reduction potentials of the nitrostilbenes [48], with electron-withdrawing groups accelerating the reaction. Moreover, when comparing the reactivity of *cis*- and *trans*-2-nitrostilbene the former, which is more difficult to reduce, reacted at a slower rate [38]. Importantly, the byproduct *o*-aminostilbene was always found only in the *trans* configuration even when starting from the pure *cis* isomer indicating an easy *cis–trans* isomerization in one of the intermediates, consistent with the decreased C=C bond order in a radical-anionic species, as independently observed [71]. Finally, the reductive cyclization of *trans*-β-nitrostyrenes affords indoles in high yields despite a *trans–cis* isomerization is necessary in order to place the nitrogen atom close to the phenyl C–H bond to be activated, a process that has been shown to be easy for 2- and 4-nitrostyrene radical anion [71].

In all cases in which metal carbonyl complexes are involved, the initial activation of the nitroarene leads to immediate formation of the corresponding nitrosoarene and CO_2. There is a general consensus on the fact that the so formed nitrosoarene is at least initially η^2-coordinated to the metal, although this has been unequivocally shown only in the case of two ruthenium complexes [13,72]. In addition, a metallacycle in which the formed CO_2 has not left the coordination sphere of the metal and has inserted in the newly formed Rh-N bond has been isolated from a reaction involving $[Rh(CO)_4]^-$ [68,69]. The point on which there is more debate is whether cyclization reactions occur at the stage of nitrosoarene or if deoxygenation proceeds up to the stage of an imido (nitrene) complex (Path (a) in Scheme 2). Little attention has been given to a further question: if the cyclization occurs at the stage of the nitrosoarene, does it involve a metal-coordinated nitrosoarene (Path (b)) or a free nitrosoarene (Path (c))?

We will first examine the evidence in favor of the involvement of nitrosoarenes at the cyclization stage and then discuss the evidence in favor of metal-imido intermediates.

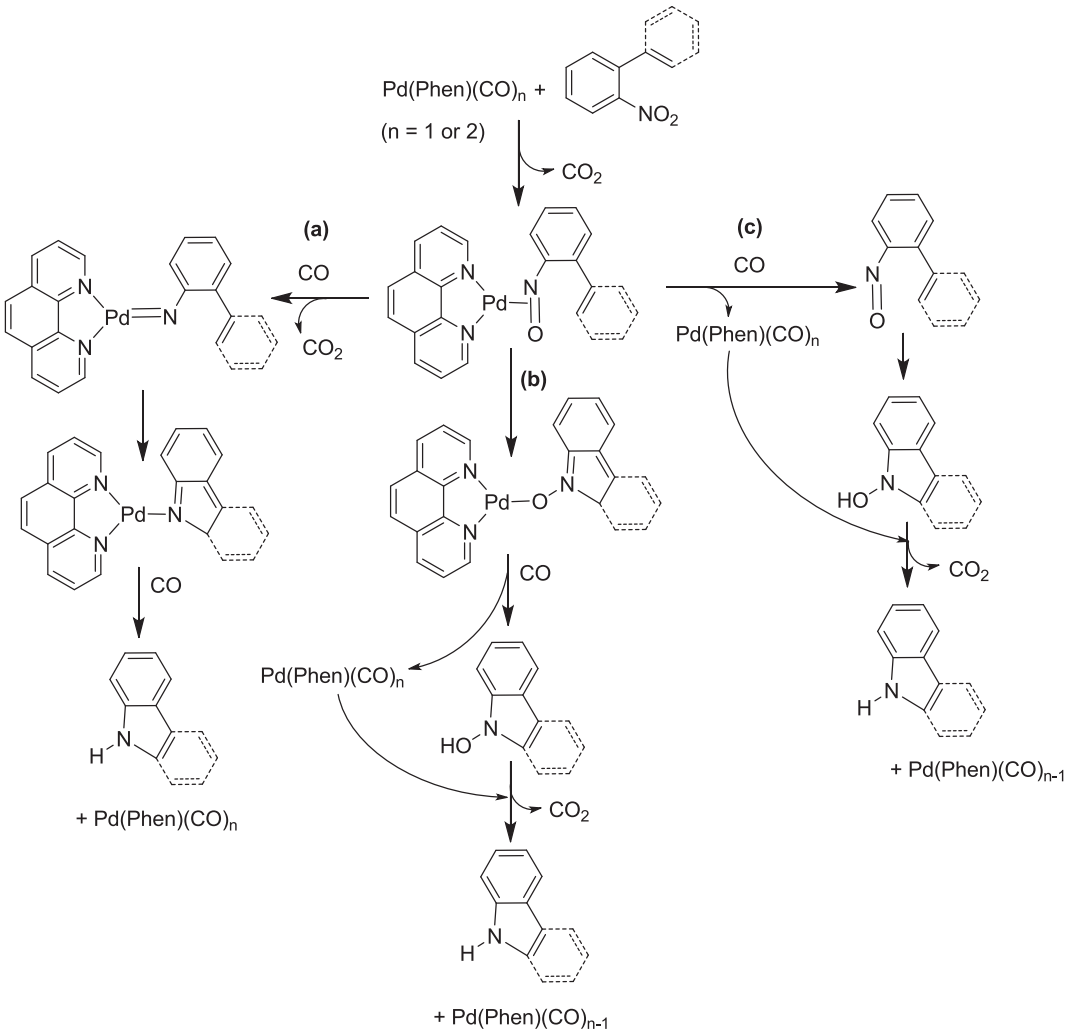
2.2. Involvement of nitrosoarenes in several reactions

Nitrosoarenes easily react with conjugated dienes in a hetero Diels-Alder reaction to give 3,6-dihydro-2*H*-[1,2]-oxazines [73] and this reaction has been long employed as a test for the formation of free nitrosoarenes in solution [74]. There cannot be any doubt that oxazine formation occurs from an intermediate nitrosoarene even when the reaction starts from a nitroarene [16,33,40,75]. However, the possibility that the reaction occurs even from a coordinated nitrosoarene cannot be discarded in general, especially when it occurs in competition with an allylic amination, as it happens in the case of a ruthenium-based catalyst [75]. However, at least as far as the Pd/Phen catalytic system is concerned, we could recently obtain a strong evidence for the involvement of free nitrosoarene in the reaction [40]. Indeed, a Pd/Phen catalyzed reduction of nitroarenes in the presence of dienes and employing phenyl formate as a CO surrogate (reaction **m** in Scheme 1) was run employing isoprene as the diene, to give mixture of the two possible regio isomers, *proximal* and *distal,* in an 88:12 ratio. When nitrosobenzene was employed as substrate under the same experimental conditions, but in the absence of any catalyst or CO surrogate, the same mixture was obtained in an essentially indistinguishable ratio: 87:13 (Scheme 3). When starting from nitrobenzene, if the reaction were proceeding through a coordinated nitrosobenzene, this should have affected the *proximal/distal* selectivity at least to some extent. The observed results strongly suggest that oxazine formation proceeds through uncoordinated nitrosobenzene even in this case.

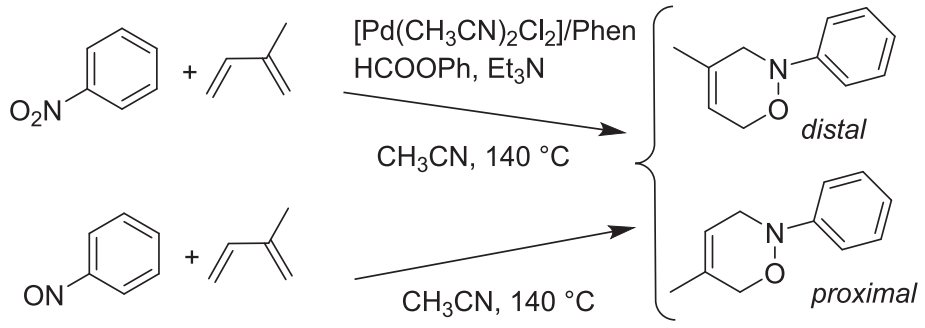
The easy formation of free nitrosoarenes during the synthesis of oxazines when a Pd/Phen catalytic system is employed strongly suggests that the former are also involved in the synthesis of indoles by the *inter*-molecular reaction of nitroarenes and alkynes (reaction **i** in Scheme 1), at least when the same kind of catalytic system is employed [18,19]. Indeed, the authors who first reported this reaction employing an iron-based catalyst [17] also showed that nitrosoarenes react with alkynes under milder conditions than nitroarenes and in the absence of any catalyst to give *N*-hydroxyindoles, which can be reduced by CO employing the same iron catalyst used in the reaction starting from nitroarenes to give indoles [76] or isolated as *N*-methoxyindoles in the presence of a methylating agent [77]. The mechanism of this easy reaction has also been studied from a kinetic and theoretical point of view [78].

As far as *intra*-molecular cyclization reactions are concerned, a clear indication that nitrosoarenes are involved, at least in a competitive pathway, at the C-N bond formation step when CO is employed as a reductant with Pd/Phen catalysts, comes from the isolation of *N*-hydroxyindoles during the reductive cyclization of *o*-nitrostyrenes [48,79,80] and of *N*-hydroxyquinolones during the reductive cyclization of *o*-nitrochalcones [79] (Scheme 4, see also reactions **a** and **b** in Scheme 1).

Theoretical evidence has also been provided that the cyclization reaction of *o*-nitrosostyrene is energetically feasible even in the absence of a metal catalyst [81]. The involvement of a nitroso compound in these two cyclization reactions cannot be experimentally tested because the corresponding compounds are not stable. In particular, attempts to obtain a nitrosostyrene derivative by oxidation of the corresponding amine led to immediate cyclization even when the reaction was run at 0 °C [82]. This high reactivity is anyway evidence that the nitroarene does not need to be completely deoxygenated to form an indole.



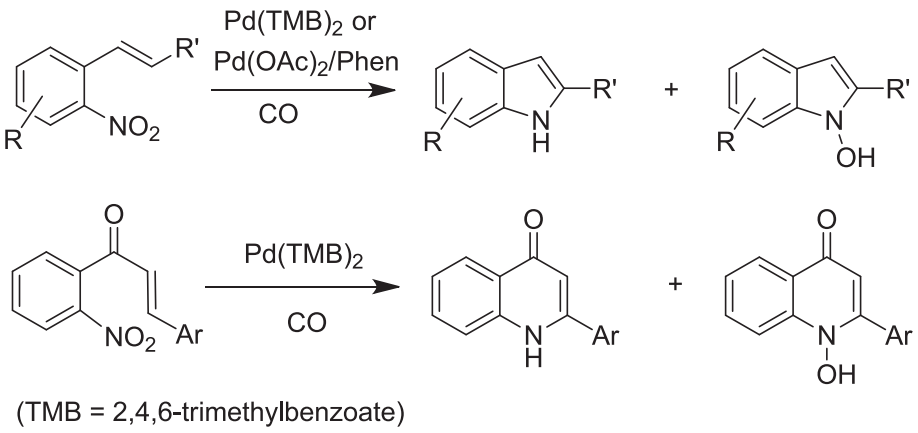
Scheme 2. Alternative pathways for the C-N bond forming step in the cyclization of *o*-nitrostyrene to indole and *o*-nitrobiphenyl to carbazole. (a) Metal-imido pathway, (b) Cyclization at the stage of a nitrosoarene complex, (c) Off-metal cyclization of a nitrosoarene. Note that only one of the possible tautomers of the intermediates was represented.



Scheme 3. Comparison between the distal/proximal selectivities observed under catalytic or standard hetero Diels-Alder conditions. Data from ref. [40].

2.3. Involvement of nitrosoarenes in the synthesis of carbazoles from o-nitrobiphenyls

Compared to the synthesis of indoles and other reactions in which the addition to a double bond is involved, the synthesis of carbazoles (**2**) by deoxygenation of *o*-nitrobiphenyls (**1**) (reaction **f** in Scheme 1) is a more difficult reaction and reduction by CO has been successful only in very few cases [1,35,83,84]. Most notably, best results were obtained using Pd/Phen catalysts [35,84]. This offers a unique opportunity to investigate the role of nitrosoarene intermediates in this reaction since,



Scheme 4. Formation of *N*-OH indoles and quinolones during reductive carbonylation reactions.

contrary to *o*-nitrososstyrenes, *o*-nitrosobiphenyls (**3**) are bench stable and their reactivity can be directly tested.

We recently reported on the use of phenyl formate as a CO surrogate for the reductive cyclization of *o*-nitrobiphenyls to carbazoles [35] and we used the reaction conditions optimized in our previous study as a reference point.

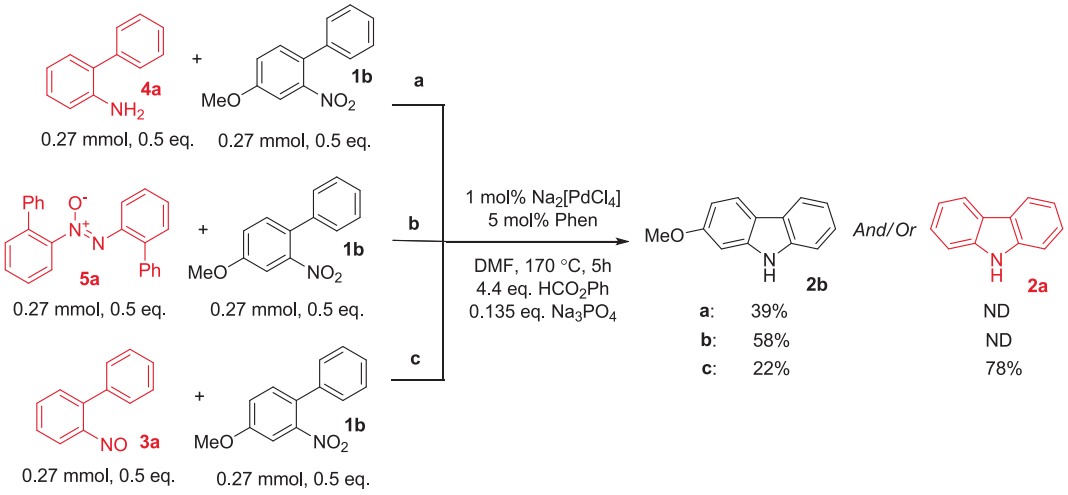
First, the possible involvement of different nitrogen compounds, containing the amino, azoxy or nitroso groups, as intermediates was investigated. In the literature, such involvement is often probed by testing the reactivity of the putative intermediate under the same reaction conditions employed for the standard reagent. In our view, this is not a correct strategy. In the field we are dealing with in this paper, for example, it has long been known that indoles can be obtained by a cyclization reaction of *o*-aminostyrenes, but an oxidant is needed to trigger the reaction [85] and at best a stoichiometric reaction with respect to the metal is to be expected in its absence. Nitroarenes can act as oxidants and anilines have indeed been found to be intermediates in reductive carbonylation reactions of nitroarenes to carbamates and diarylureas in all cases in which this possibility has been tested, including the reactions catalyzed by Pd/Phen systems [86–88]. The best way of testing the possible involvement as intermediates of different nitrogen compounds in our reaction is to investigate their reactivity under the standard reaction conditions and in the presence of a nitroarene bearing different substituents on the aryl ring. This way, all relevant organic and organometallic species are surely present during the reaction and the origin of the obtained products can be back-traced. One of us has previously employed this strategy to test the possible involvement of anilines in the reductive cyclization of *o*-nitrostyrenes to indoles with different metal catalysts [89]. Relevant to the present work, when a Pd/TMPhen (TMPhen = 3,4,7,8-Me_4Phen) was employed, only a small amount of aniline derived indole was obtained (*ca.* 5% of that derived from the nitroarene), indicating that anilines can at best be involved in a minor competitive pathway in a standard catalytic reaction, where the aniline concentration would be much smaller.

We thus performed three reactions in which *o*-nitrosobiphenyl (**3a**), *o*-aminobiphenyl (**4a**) and the corresponding azoxyarene (**5a**) were reacted under standard reaction conditions in the presence of an equimolar amount of 4-methoxy-2-nitro-1,1′-biphenyl (**1b**) (Scheme 5).

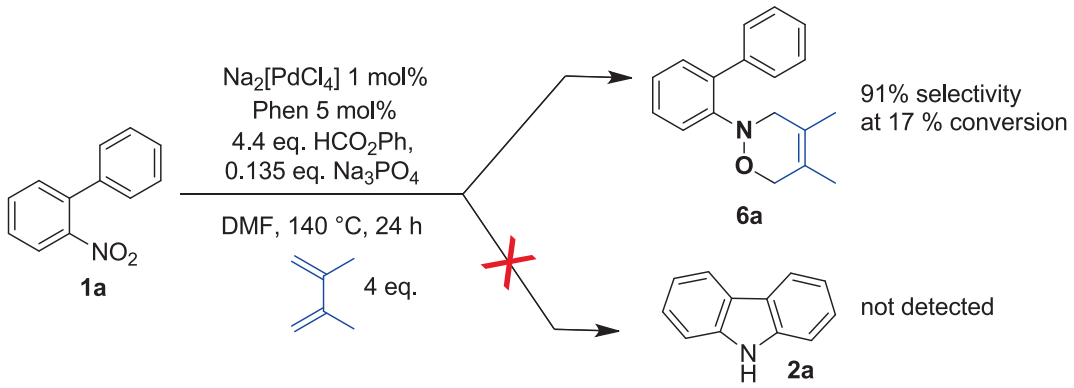
Only the nitroarene-derived carbazole could be detected when the reaction was run in the presence of the amine or azoxy derivative, proving that neither is involved as an intermediate in the reaction. However, when the nitrosoarene was present, not only did it afford the corresponding carbazole, but it did so in an even higher yield than the nitroarene, supporting its role during the reaction.

To ascertain if **3a** is present as a free molecule during a standard catalytic reaction or if it remains coordinated to the metal, a catalytic reaction was run in the presence of 2,3-dimethylbutadiene (Scheme 6). The temperature had to be lowered to 140 °C because we have previously found that oxazines tend to decompose to pyrroles at higher temperatures [16,75].

The reaction was quite slower at this reduced temperature and only a 17% conversion of **1a** was obtained after 24 h, but the only product obtained, 91% selectivity, was the corresponding oxazine **6a**. No carbazole was observed. Coupled with the conclusions on the



Scheme 5. Competitive experiments with potential intermediates. Isolated yields for **2b** and GC yields for **2a** are reported. ND = not detected.



Scheme 6. Trapping of intermediately formed **3a** by 2,3-dimethylbutadiene.

mechanism of oxazine formation discussed in paragraph 2.2, this experiment clearly proves that uncoordinated **3a** is formed during the reaction. Although it cannot be experimentally excluded that **3a** leaves the coordination sphere of the metal just to reenter it before C–H activation and ring closure occur, this appears to be a very unlikely scenario. Thus, the experiment strongly indicates that the reaction proceeds through the intermediate formation of uncoordinated nitrosobiphenyl, which then further evolves in an off-metal reaction towards carbazole, in competition with a faster trapping by a conjugated diene to give an oxazine.

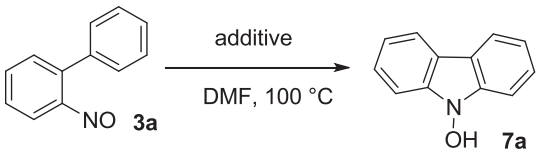
2.4. *Reactivity of o-nitrosobiphenyl: Experimental studies*

The reactivity of **3a** was investigated by measuring the kinetics of its cyclization reaction. It should be recalled that **3a**, as most nitrosoarenes, is present in the solid state as a colorless dimer with a N-N bond (an azodioxyarene) [90]. However, it equilibrates with the monomeric compound when dissolved and in dilute solutions, only the monomer is virtually present. The latter is blue colored and this allows monitoring the reaction by UV–Vis spectroscopy (λ_{max} = 770 nm in DMF) without interference from other possible products. The reaction does not proceed at RT, but it is too fast at 170 °C, so an intermediate temperature, 100 °C, was chosen for this study (Scheme 7).

In order to minimize contamination and any perturbation of the system, the reaction was run in a sealed two-chamber apparatus in which one of the two chambers is made of optical glass and the solution can be moved from one chamber to the other by tilting it, without any need to withdraw samples of the solution to record the UV–Vis spectrum. A picture of this piece of glassware is reported in the Supplementary Material.

By plotting the logarithm of the absorbance at 770 nm of the solution against time (Fig. 1) an almost perfect (R^2 = 0.9995) linear correlation was obtained, proving the reaction is first order in **3a** and allowing calculation of its rate constant: 0.23 h^{-1}.

Then we repeated the measurement in the presence of several substances (1 eq. with respect to **3a**) that are present in the catalytic system or could occur as impurities during catalytic reactions, including Phen, water, and a palladium(II) phenanthroline complex. The study was extended to the addition of either acetic acid or two acetate salts, because Smitrovich and Davies reported, in their study on the reductive cyclization reaction of *o*-nitrobiphenyls to carbazoles catalyzed by a Pd/



Scheme 7. Reaction involved in the kinetic study.

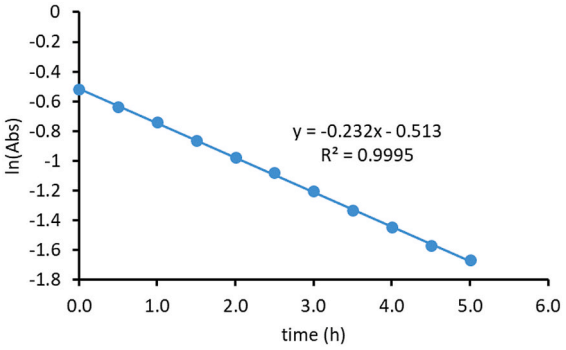


Fig. 1. Logarithmic plot of the absorption at 770 nm over time of a solution of **3a** (10.0 mg, 0.055 mmol, in 5 mL DMF) heated at 100 °C.

Phen systems, that the presence of acetate as the counteranion for palladium was essential to achieve high catalytic activity [84]. When investigating the same reaction employing phenyl formate as a CO surrogate [35], we did not find an analogous requirement for the presence of acetate, but the effect of its presence on the reactivity of **3a** was anyway worth of investigation. All the reactions followed a first order kinetics in **3a** and their rate was almost indistinguishable from that of the unpromoted reaction in all but one case. Only the addition of triethylamine notably boosted the reaction, which still remained first order in **3a** (Fig. 2). All kinetic plots are reported in the Supplementary Material (Fig. S2). The reaction in the presence of acetic acid was also performed by adding 5 equiv. of acid, but no significant variation was noticed (k = 0.24 h^{-1}).

In all reactions employing phenyl formate or the formic acid/acetic anhydride mixture as CO surrogates, a base is required to promote CO release [5,91–94] and we have most often employed Et_3N for this purpose. However, it should be noted that the addition of bases has been previously found to be beneficial for many, albeit not for all, reductive cyclization reactions of nitroarenes employing CO as the reductant, including those in which pressurized CO was employed and no need for the decomposition of its surrogate would be present [7]. The role of bases in these cases has never been clarified. In the case of the synthesis of carbazoles, we found that at the temperature required, 170 °C, a temperature higher than that employed in all other cases previously investigated by us, Et_3N acted as a hydrogen source to reduce the nitro group to amino, leading to the formation of large amounts of **4a** as byproduct. The problem could be solved by employing inorganic bases instead, best Na_2CO_3 and Na_3PO_4. However, the latter compounds are sparingly soluble in DMF at RT, where the UV–Vis spectrum is recorded, and are thus not suitable for a kinetic study. We thus resorted to using Et_3N instead, which anyway gives no decomposition problem at 100 °C and in the absence of any metal.

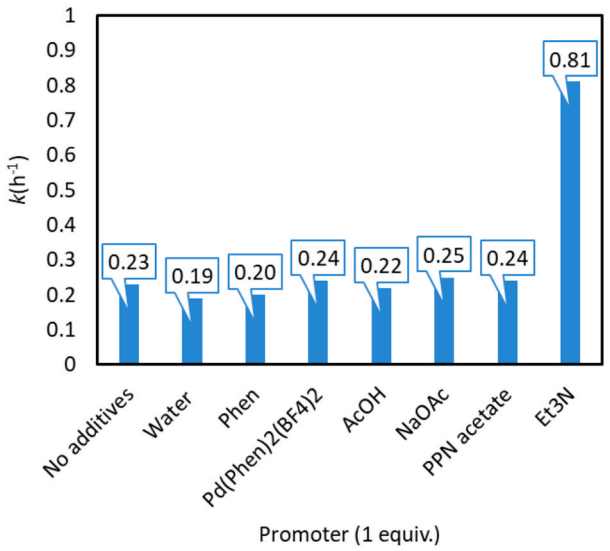


Fig. 2. Effect of several additives on the rate of the reaction in Scheme 7 (In case of water, a larger amount was employed, 20 μL, 20 equiv.). ($PPN^+ = (Ph_3P)_2N^+$).

Having identified the positive action of triethylamine on the reaction of *o*-nitrosobiphenyl, we investigated the effect of changing its concentration. All reactions remained first order in **3a** (see SM for the corresponding plots, Fig. S3), so that the pseudo first order constant for each reaction can be compared (Fig. 3).

The rate is clearly first order ($R^2 = 0.9982$) with respect to Et_3N up to a 0.11 M concentration (10 eq. with respect to **3a**) and then suddenly flattens, a behavior typical of a change in the rate determining step. This result not only confirms the existence of a second role of the base in the reaction mechanism apart from that of activating phenyl formate, but also allows us to identify at which stage of the reaction the base is involved. Although the present results do not exclude that the base also acts in different ways in related catalytic reactions other than the synthesis of carbazoles, it must be remarked that this is the first time that a specific positive role of a base is clearly identified in a reductive cyclization reaction of nitroarenes with CO as the reductant.

The kinetic measurements were performed by recording the disappearance of **3a**. Cyclization is supposed to yield *N*-hydroxycarbazole (**7a**) but this kind of derivative appears to have a limited stability. Only a handful have apparently been isolated in a pure form many years ago [95], among which **7a** was isolated in only 1% yield. A reaction was performed for synthetic purposes (Scheme 8).

A GC–MS analysis of the reaction mixture after complete consumption of **3a** allowed indeed to detect the formation of **7a**, although together with **4a** and **5a**. Pure **7a** could not be isolated.

With the goal of obtaining stronger evidence of the formation of an

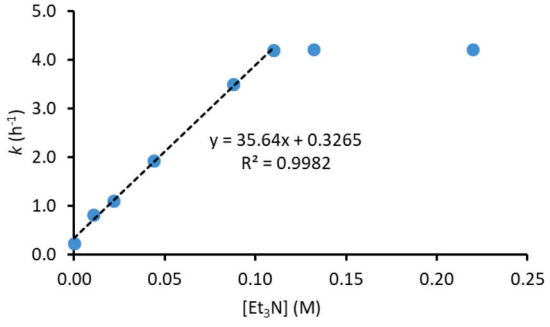


Fig. 3. Rate of the reaction in Scheme 7 as a function of the concentration of Et_3N.

N-hydroxycarbazole as the primary product of cyclization of *o*-nitrosobiphenyl, we pursued a strategy to stabilize this elusive intermediate. Our approach was to run the cyclization of the methoxy-substituted analogue, 4,4′-dimethoxy-2-nitroso-1,1′-biphenyl (**3c**) to yield 2,7-dimethoxy-*N*-hydroxycarbazole (**7c**), which we predicted to have a lower reactivity with respect to the excess triethylamine because of the inductive effect of the methoxy groups. Moreover, during our studies on the synthesis of carbazoles [35], we had noted that 2,7-dimethoxy-9*H*-carbazole (**2c**) is remarkably poorly soluble with respect to other carbazoles. Assuming that the same would hold for **7c**, this fact should facilitate its purification. Fortunately, our hypothesis was decisively confirmed by the successful isolation of the target **7c** in 98% yield (Scheme 8), providing direct evidence for the formation of this kind of intermediate during catalytic carbonylation reactions.

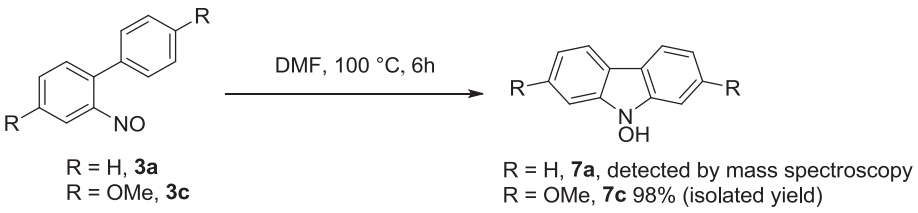
2.5. Reactivity of *o*-nitrosobiphenyl: theoretical studies

The cyclization reaction of **3a** to **7a** has been previously briefly investigated by theoretical methods [81]. The reaction was proposed to involve a series of hydrogen shifts, one of which has a very high $\Delta H^{\ddagger}$ of 43.6 kcal/mol (Scheme 9). The possibility that bases may play a role in the reaction was mentioned, but not investigated theoretically.

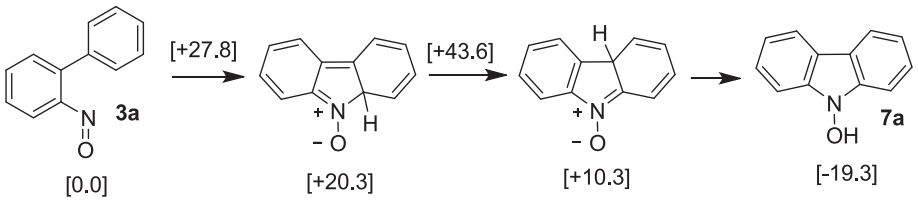
In order to investigate from a theoretical point of view the now experimentally proven role of bases in the cyclization reaction of **3a** to **7a**, in a consistent way, both the base-free and the base-promoted reactions were reinvestigated. The possible involvement of DMF in the reaction was also considered.

The study of the reaction mechanism in the absence of the base, at the M06/6–311++G(d,p)(GD3)(DMF)// PBE0/6-311G(d,p) level of theory, led to the free energy profile reported in Fig. 4 (See experimental section for computational details). According to our findings, after the cyclization transition state (TS) (**3a-[I-II]**$^{\neq}$) featuring $\Delta G = 27.8$ kcal/mol, the minimum energy pathway should require the proton transfer from the α to the β carbon in order to give intermediate **3a-III**, as any attempt of direct proton transfer from the α carbon to the oxygen failed. This proton transfer TS (**3a-[II-III]**$^{\neq}$) is characterized by a high free energy ($\Delta G = 34.3$ kcal/mol), although not as prohibitive compared to the ΔH reported for the previously investigated mechanism in Scheme 9. The last proton transfer, from the β carbon to the oxygen occurs through a 5-membered cyclic TS (**3a-[III-IV]**$^{\neq}$) of 26.5 kcal/mol, to give product **7a**.

In the reaction mechanism shown in Fig. 4, the highest barrier to overcome according to the energy span model [96] is of 34.3 kcal/mol, corresponding to the energy gap between **3a-[II-III]**$^{\neq}$ and the starting substrate **3a-I**. Nevertheless, very often proton transfers are assisted by molecules acting as proton shuttles. In this view, DMF could play a very important role in the reaction mechanism. Consequently, the cyclization of **3a** to **7a** was investigated in the presence of an explicit molecule of DMF. The calculated free energy profile is depicted in Fig. 5. Starting from **3a-I**, an entropic cost has to be paid in order to get the bimolecular intermediate **3a-I-DMF** ($\Delta G = 6.5$ kcal/mol). Nevertheless, an electrostatic interaction between DMF and the proton that should be transferred (in green) is calculated during the cyclization containing the increase in the TS energy (for **3a-[I-II]-DMF**$^{\neq}$ $\Delta G = 30.6$ kcal/mol), as well as the energy of the resulting intermediate **3a-II-DMF** ($\Delta G = 23.2$ kcal/mol). The following attempt to transfer the hydrogen unexpectedly led to a very stable intermediate at −3.3 kcal/mol (**3a-III-DMF**), arising from the addition of DMF to the substrate, as well as the recovery of the substrate aromaticity. The calculated TS shows a low barrier ($\Delta\Delta G = 5.3$ kcal/mol) due to the 6-membered cyclic geometry involved in the proton transfer. The following proton transfer to the substrate oxygen proceeds with a low barrier, as well through **3a-[III-IV]-DMF**$^{\neq}$ TS, giving the desired product and the DMF molecule is regenerated. An alternative pathway, involving a proton transfer to the β carbon (**3a-[III-IV]'-DMF**$^{\neq}$) followed by the transfer to the substrate oxygen (**3a-[IV-V]'-DMF**$^{\neq}$), is associated to higher energy and is depicted in light grey



Scheme 8. Identification of *N*-hydroxycarbazoles.



Scheme 9. Previously reported [81] B3LYP/6–31 + G*-optimized geometries and energies (ΔH for intermediates and $\Delta H^{\ddagger}$ for the transition states) for the 1,5-electrocyclization of **3a**. Energies are given in kcal/mol.

in Fig. 5.

According to these findings, in the absence of any other additive, DMF directly participates to the reaction, playing a key role in the formation of **7a**. The cyclization reaction of *o*-nitrosobiphenyl is unlikely to be the rate determining step of the overall catalytic process starting from the nitroarene, but it should anyway be recalled that the latter proceeds much better in DMF than in other solvents, including other polar aprotic ones such as acetonitrile. It is well known that DMF can be involved in several reactions and its moieties are found in the final products [97]. However, DMF is also a key solvent for many reactions, but the reasons for which this is the case are generally obscure. The result from the calculations that DMF actually undergoes a proton-transfer reaction by forming a transient dimethylformamide hemiacetal-type intermediate represents, to the best of our knowledge, an unprecedented role for DMF, which may be of much broader relevance. Note also that in the related cyclization of *o*-nitrostyrenes to indoles employing phenyl formate as a CO surrogate [38], the best yields were obtained by employing a CH_3CN/DMF 9:1 mixture as solvent. The significant activity increase by the addition of just a minor amount of DMF speaks for a role of the latter other than that of a simple polar solvent, although no clue about its actual effect could be gained at the time. Nevertheless, a direct involvement of DMF during the reaction is likely.

To rationalize the increase of the reaction rate in the presence of Et_3N, the modification of the energy profile was investigated in the presence of this base. As shown in Fig. 6, the replacement of DMF with Et_3N, slightly lowers the free energy cost of the adduct formation giving a more stable intermediate, due to stronger H-bond interaction (N•••H distance is 2.48 Å). The located amine assisted cyclization TS (**3a- [I-II] - $Et_3N^{\neq}$**) is associated with ΔG = 26.7 kcal/mol. After this TS, the system directly drops to product **7a**, as the amine assists the proton transfer to oxygen. Any attempt to locate other minimum energy intermediates in-between **3a- [I-II] - $Et_3N^{\neq}$** and the product failed. The SCF energy profile is reported in Fig. S28.

In summary, the cyclization of **3a**, likely occurs with a direct participation of DMF in the absence of other bases, with an energy span of 30.6 kcal/mol, and accelerates when introducing Et_3N, with an energy span of 26.7 kcal/mol, thanks to the improved H-bond interaction. The presence of the amine not only lowers the cyclization TS energy but allows to skip the following hydrogen transfer, accompanied by the loss of the substrate aromaticity as well.

At 100 °C (373 K) in DMF the experimental value of the first order kinetic constant is 0.223 h^{-1} = 6.19 10^{-5} s^{-1}. From the calculated value of $\Delta G^{\ddagger}$ (30.6 kcal/mol) and employing the Eyring equation (assuming that the transmission coefficient is unity) [98] the value $k = 0.915\ 10^{-5}$ s^{-1} at 373 K is obtained for the unpromoted reaction.

A comparison with the kinetic constants for the base-catalyzed reactions should be made with caution because whereas the uncatalyzed reaction is purely first order, the base-catalyzed one is only pseudo-first order under the investigated conditions. With this limitation in mind, it is possible to note that the maximum experimental pseudo-first order rate constant in the presence of Et_3N is 4.21 h^{-1} = 1.17 10^{-3} s^{-1}. From the DFT value of $\Delta G^{\ddagger}$ (26.7 kcal/mol), one can calculate the value of k = 1.76 10^{-3} s^{-1} at 373 K), that is of the same order of magnitude of the experimental k.

Although the DMF-assisted mechanism underestimates the reaction rate of about half order of magnitude, the agreement between the experimental and theoretical data strongly supports the hypothesis that the reaction actually proceeds as described.

2.6. *The possible involvement of imido complexes*

As an alternative to nitrosoarenes, metal-imido complexes (sometimes improperly named nitrene complexes) have also been often claimed as intermediates in the reductive cyclization reactions of nitroarenes. The proposal clearly originates from the observation that the same final cyclized organic products can be obtained by reaction of the corresponding arylazides [3] and that metal-imido complexes can indeed be formed employing these reagents [99–102] and be active in cyclization reactions. However, the evidence for the involvement of imido species in reactions of nitroarenes is much weaker and questionable.

In the field of the synthesis of carbazoles, the only evidence for the involvement of imido complexes comes from a study of Cenini and coworkers in which a ruthenium cluster containing two bridging imido groups derived from *o*-nitrobiphenyl, $[Ru_3(CO)_9(\mu_3\text{-}(2\text{-}Ph\text{-}C_6H_4N)_2]$, afforded carbazole when heated at 220 °C under 50 bar CO, albeit in only 9% yield, the main product being *o*-aminobiphenyl (89%) [83]. This cluster is a member of a wider family of trinuclear ruthenium [103–107] or iron [65,108] clusters bearing one or two μ_3-NAr groups, which can be easily obtained by reaction of $Ru_3(CO)_{12}$ or $Fe_3(CO)_{12}$ with nitroarenes. These clusters have also been proposed to be intermediates in the carbonylation reaction of nitroarenes to carbamates (for the ruthenium ones) [109] or their reduction by CO/H_2O to give anilines [110] (in the case of iron complexes). However, we have since demonstrated that ruthenium clusters do not play any role in the former reaction [111,112] and that imido-iron clusters are not involved in the latter [65,66]. Thus, it is extremely unlikely that $[Ru_3(CO)_9(\mu_3\text{-}(2\text{-}Ph\text{-}C_6H_4N)_2]$ or any related species is actually formed under the real

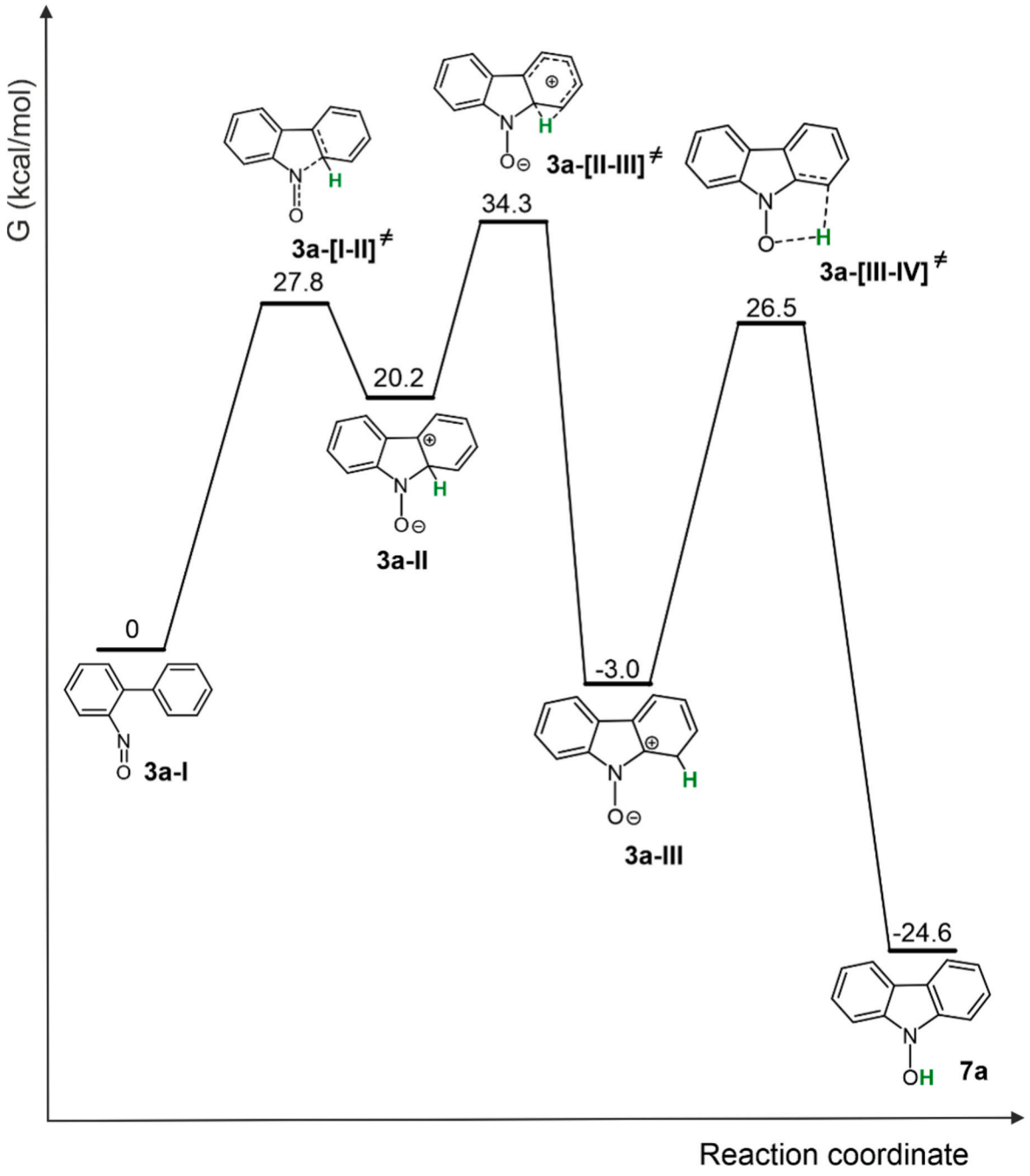


Fig. 4. Free energy profile for the cyclization mechanism of *o*-nitrosobiphenyl (**3a**), calculated at the M06/6–311++G(d,p)(GD3)(DMF)// PBE0/6-311G(d,p).

catalytic conditions in which the $Ru_3(CO)_{12}$ catalyzed reductive cyclization of *o*-nitrobiphenyl to carbazole by CO is performed.

Regarding palladium catalysis in general, it should be noted that mononuclear palladium imido complexes of the kind proposed in the literature have only been recently isolated and that this was only possible by employing sterically encumbered cyclic alkylaminocarbene ligands (CAAC) [113,114] that are very different from the ligands employed in the reactions of nitroarenes.

In the field of reductive reactions of nitroarenes by CO, palladium imido complexes were first proposed to be intermediates in the Pd $(PPh_3)_2Cl_2/SnCl_2$ catalyzed reaction of *o*-nitrostyrenes to indoles and in that of nitrobenzene with benzaldehyde to give the imine PhN=CHPh [115]. However, we have already shown that at least the latter reaction proceeds by the action of trace amounts of water, which, together with CO, generate aniline from nitrobenzene. Aniline then condenses with benzaldehyde to give the observed imine and regenerates the water necessary to restart the catalytic cycle [89]. Thus, the direct involvement of an imido complex in the C-N bond formation is excluded at least for this reaction.

An apparently strong piece of evidence for the involvement of palladium imido complexes during reduction reactions of nitroarenes by CO comes from a carbonylation reaction of nitrobenzene to methyl phenylcarbamate that was run in the presence of cyclohexene. The catalyst was generated *in situ* by reacting palladium acetate with a chelating diphosphine, $(2\text{-}MeOC_6H_4)_2P(CH_2)_3P(2\text{-}MeOC_6H_4)_2$. GC–MS analysis of the solution after the reaction allowed to detect the formation of a product with a parent mass peak at $m/z = 173$, which was attributed to the corresponding aziridine (7-phenyl-7-aza-bicyclo-[4.1.0]heptane) [116]. Since the formation of imido complexes in these reactions is in contrast not only with the studies reported above in this work, but also

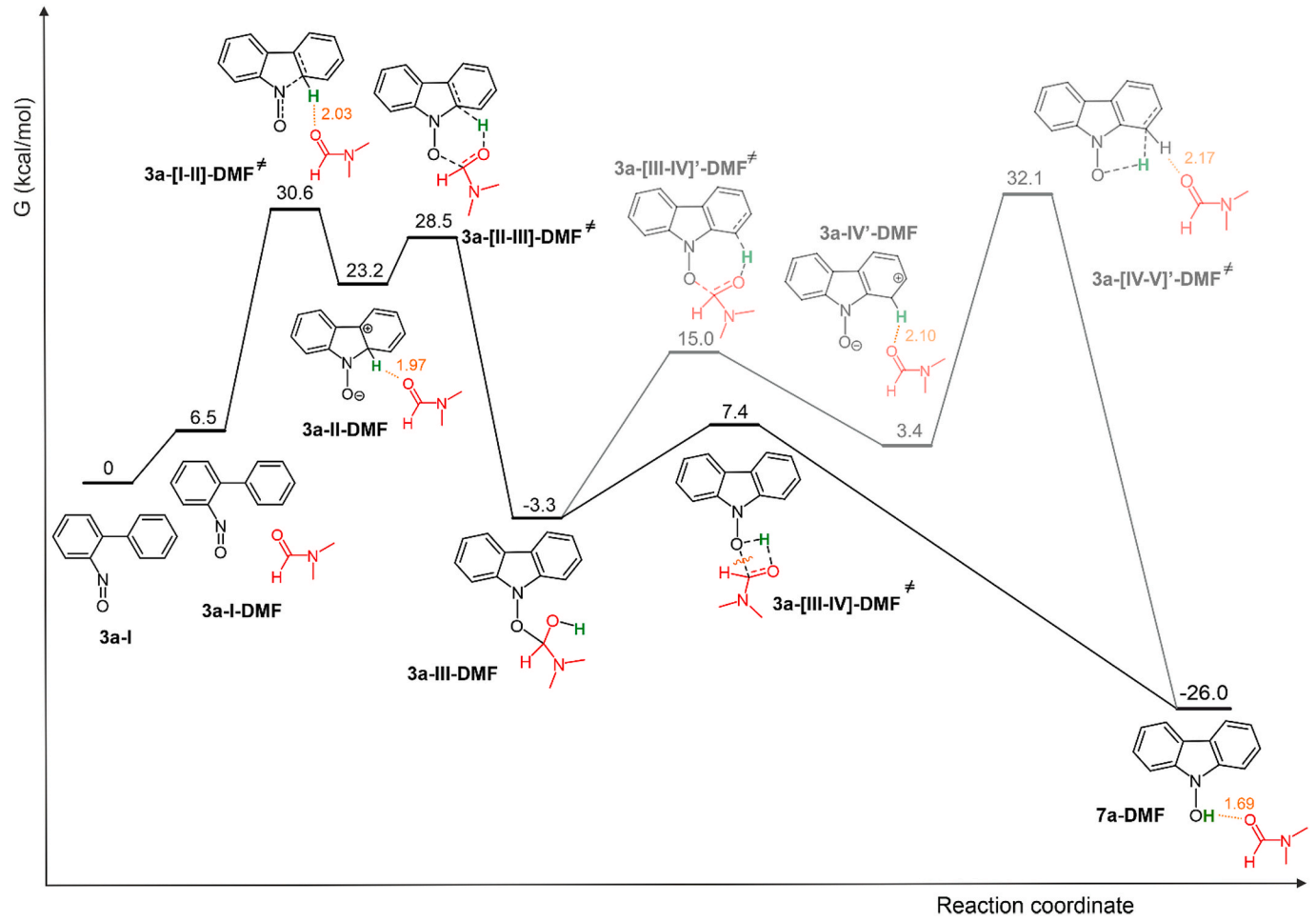


Fig. 5. Free energy profile for the cyclization mechanism of *o*-nitrosobiphenyl (**3a**) assisted by DMF, calculated at the M06/6–311++G(d,p)(GD3)(DMF)// PBE0/6-311G(d,p).

with our mechanistic studies of the carbonylation of nitroarenes to give methyl arylcarbamates with palladium/phenanthroline catalysts [88], we reproduced this reaction. The only difference with respect to the published reaction is that we employed commercially available 1,3-*bis* (diphenylphosphino)propane as ligand, which lacks the methoxy groups (Scheme 10).

We indeed observed by GC–MS analysis the formation of the same product reported in [116] (virtually identical mass spectrum, see Fig. S4), but the compound is not an aziridine. It is an allylic amine (*N*-(cyclohex-2-en-1-yl)aniline), as shown by a comparison with an independently synthesized sample (same retention time and identical mass spectrum; see Fig. S5). The possibility that the product was an allylic amine, with the same mass as the aziridine, was apparently not taken into consideration in the original work. This result was not surprising to us because we have already investigated the allylic amination of cyclohexene by nitroarenes under CO pressure many years ago [13,117]. Although the best catalysts are based on ruthenium carbonyls in the presence of Ar-BIAN (Ar-BIAN = *bis*-(arylimino)acenaphthene) [13,117] or iron catalysts [14,15], in our papers we had additionally reported that a palladium catalyst (palladium trimethylbenzoate with a phenanthroline ligand) also gave the allylic amine, but in much poorer yields. The fact that the product is an allylic amine instead of an aziridine does not completely exclude the involvement of imido complexes in the reaction – allylic amine may even result from a rearrangement of an intermediately formed aziridine under the reaction conditions–, but undermines the validity of the experiment in proving that they are active intermediates. Indeed, allylic amines can also be formed by the well-known nitroso-ene reaction [118,119], followed by deoxygenation, a reaction that can occur even in the absence of a metal catalyst, but which is greatly facilitated by a range of metal catalysts and for which nitrosoarene complexes have been identified as the key aminating species in several cases [120–124]. Thus, the observed results cannot be held as proof of the formation of an $L_nPd{=}NAr$ complex. Note that the same test has also been employed by Xia, Li and coworkers to investigate the possible formation of imido complexes during a Pd-catalyzed reductive aminocarbonylation of olefins with nitroarenes [125]. In this case, 3-chloro-nitrobenzene was employed as substrate, again with cyclohexene as the olefin, and the formation of a product having a mass spectrum compatible with that of the corresponding aziridine was observed and attributed to this compound. We did not reproduce this experiment, but the similarity of the fragmentation pathway of the reported compound with that of 3-phenyl-cyclohexene (all peaks being shifted at a higher *m/z* ratio because of the presence of chlorine) strongly suggests that an allylic amine was obtained even in this case. The formation of an aziridine under the conditions of this last work would be anyway surprising because all other experiments were run in the presence of styrenes and aziridines were not reported among the products. This should not be the case because styrenes are typical substrates for aziridination reactions by catalytic systems in which a metal-imido species is surely formed, as when aromatic azides [101,126] or aryliminoiodinanes [127] are employed as reagents. The formation of aziridines has been found to be even easier for styrenes with respect to aliphatic olefins [128].

In conclusion, we have shown that the few experiments previously

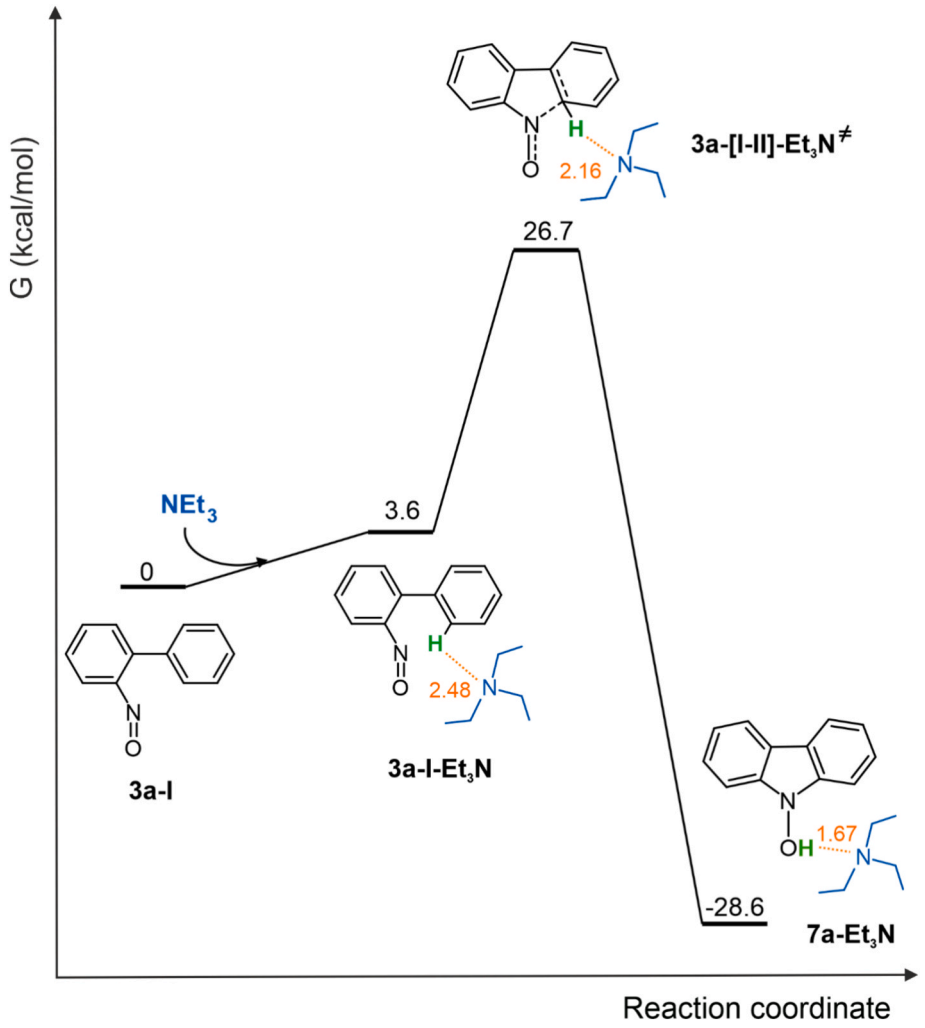
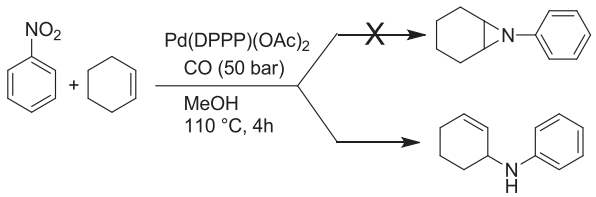


Fig. 6. Free energy profile for the cyclization mechanism of *o*-nitrosobiphenyl (**3a**) assisted by Et_3N, calculated at the M06/6–311++G(d,p)(GD3)(DMF)// PBE0/6-311G(d,p).



Scheme 10. Trapping experiment with cyclohexene. DPPP = 1,3-bis(diphenylphosphino)propane.

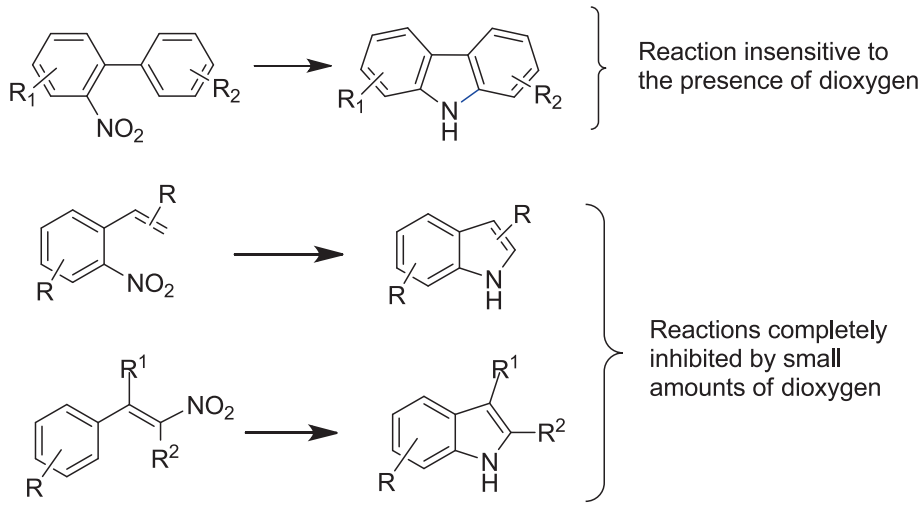
considered as evidence in favor of the involvement of imido complexes in reductive reactions of nitroarenes by CO cannot be employed to support this view. This does not obviously mean that imido complexes are never formed even when other reducing agents are employed; however, we are not aware of any experiment that strongly supports their involvement in any nitroarene-based reaction.

2.7. The resting state of the catalytic cycles

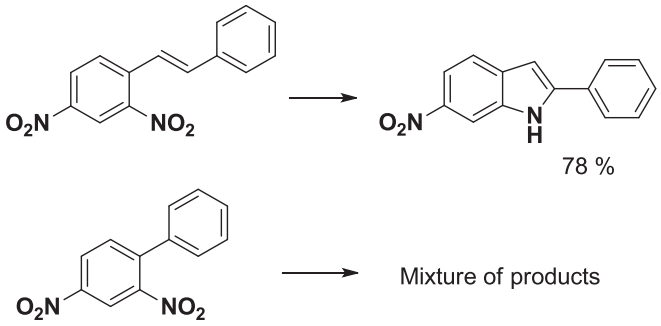
From the work described in the previous sections, we have gained strong evidence for an active role of uncoordinated nitrosoarenes at the critical C-N bond formation stage, while the involvement of metal-imido species is unlikely and can be ruled out. At this stage, it may appear that little remains to be said. The role of the catalyst is twofold and the same for all reactions in this class: first deoxygenate the nitro group to nitroso; second deoxygenate the *N*-hydroxy group formed upon cyclization outside the coordination sphere of the metal to N–H. The different temperatures required to foster different cyclization reactions would only reflect their activation energies. Still, something is not explained by this simple description. At least under the conditions of the protocols developed by us, the cyclization of *o*-nitrobiphenyls to carbazole [35] is insensitive to the presence of air, whereas those of *o*-nitrostyrenes [38] or β-nitrostyrenes [37] to indoles are extremely sensitive to even trace amounts of dioxygen. The effect is not due to the easier oxidation of indoles compared to carbazoles because otherwise only the selectivity would be affected. On the contrary, the reaction is completely inhibited in the last two cases (Scheme 11).

To explain the different oxygen sensitivities of these apparently very similar reactions we made a working hypothesis: the resting state of the catalyst during the carbazole synthesis is an oxygen-insensitive palladium(II) complex, whereas in indole syntheses it is, in both cases, a highly oxygen sensitive palladium(0) one. A clue as to which may be the palladium(0) complex involved in the latter case comes from a comparison of the reaction selectivities observed when dinitro compounds are employed as reagents (Scheme 12).

Whereas the cyclization of 2,4-dinitrostyrene gave selectively the corresponding indole [38], that of 2,4-dinitrobiphenyl afforded a mixture of products in which little, if any, nitrocarbazole was present [35]. The result of the latter reaction was not unexpected, as it is well



Scheme 11. Sensitivity of different reductive cyclization reactions to oxygen.



Scheme 12. Reductive cyclization reactions of dinitroarenes.

known that the presence of a substituent in the *ortho* position with respect to the nitro group tilts the latter out of the plane of the aryl ring and makes its reduction more difficult [129]. Coming to the catalytic system here employed, we have previously shown that when 2,4-dinitrotoluene is carbonylated to the corresponding methyl dicarbamate by a Pd/Phen catalyst and the reaction is stopped before completion, the nitro group in the position 4 is carbonylated to a much larger extent than that in the position 2 over a range of experimental conditions [130]. The fact that the reduction of the *ortho* nitro group proceeds much more rapidly than that of the *para* one for the styrene derivative indicates that the olefinic group has a positive orienting effect on the reaction. Based on the stability against palladium black formation, we and others have already proposed that the olefin groups may coordinate to palladium before the reduction occurs [7,80] and the observed selectivity supports this hypothesis. However, no direct evidence in favor of this proposal has ever been reported.

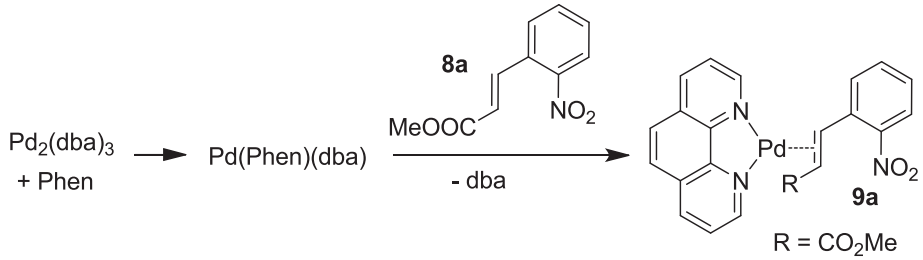
We thus engaged in a study to prove that such complexes are indeed formed during the catalytic reaction. A few palladium(0) complexes are known to have phenanthroline or its substituted analogues as ligands and with olefins bearing electron-withdrawing substituents [131–138]. First of all, we targeted the independent synthesis of the complex bearing methyl (*E*)-2-nitrocinnamate (**8a**) as the ligand. This olefin was chosen because it was the one employed in our optimization studies of the synthesis of indoles and because the presence of an electron-withdrawing substituent has, up to now, proved essential in order to allow isolation of Pd(0) olefin complexes with nitrogen ligands.

Pd(Phen)(**8a**) (**9a**) was obtained by reaction of *in situ*-generated Pd(Phen)(dba) (dba = dibenzylideneacetone) [138] with **8a** (Scheme 13).

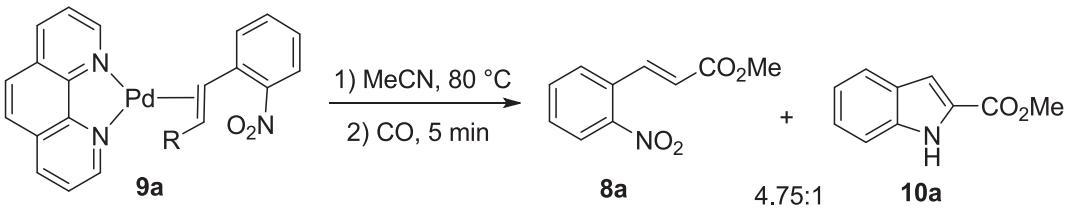
Many attempts to grow single crystals of **9a** suitable for X-ray diffraction analysis were made. In the end, the best, albeit of limited quality, crystals could be obtained by slow diffusion of hexane into the acetone solution employed for the synthesis of the complex. Its crystal structure is described in paragraph 2.8. Note that although the complex can be obtained as a solid and is stable as such at least for several weeks under a dinitrogen atmosphere, it is only stable in solution in the presence of excess **8a**.

Complex **9a** was dissolved under a dinitrogen atmosphere in acetonitrile, the solvent we most often used for the synthesis of indoles from *o*-nitrostyrenes, and the solution quickly heated to 80 °C. At this point, CO (1 atm) was allowed into the Schlenk tube containing the hot solution. Within 5 min a precipitate of palladium black was observed and GC analysis of the solution evidenced the presence of **8a** and of the expected indole (**10a**) in a molar ratio 4.75:1 (Scheme 14).

The results clearly show that **9a** can produce the indole **10a** upon reaction with CO, but also that its coordination to palladium is reversible. Note that the low indole yield in this stoichiometric reaction is due, at least in part, to the instability of **9a** in the absence of excess **8a** and to the fact that, under catalytic conditions, a higher CO pressure is present, that we could not reproduce in a stoichiometric test.



Scheme 13. Synthesis of the palladium(0) olefin complex **9a**.



Scheme 14. Reactivity of **9a**.

To complete the picture, it is necessary to prove that Pd(Phen) (nitrostyrene) complexes are indeed present as the resting state under reaction conditions. The task is not easy because the reactions are run under CO pressure, preventing a direct analysis of the solution with a standard apparatus. Moreover, the catalyst amounts employed under typical conditions (1 mol% or less) are too low to allow for the isolation of any metal complex and when the catalyst loading is increased significantly, the reaction quickly proceeds to the end, with formation of metallic palladium. The latter is the typical metal-containing species observed when the nitroarene is completely consumed, since palladium (0) carbonyl complexes with nitrogen ligands are not stable.

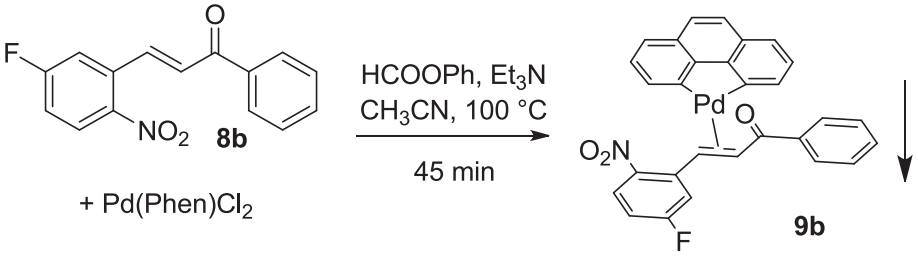
Several attempts to isolate **9a** from a catalytic reaction solution failed, but when (*E*)-3-(4-fluoro-2-nitrophenyl)-1-phenylprop-2-en-1-one (**8b**) was employed as the substrate, layering with diethyl ether the solution of a catalytic reaction stopped before its completion allowed us to obtain some single crystal of **9b** of sufficient quality for a structural characterization (Scheme 15). Its crystal structure is described in paragraph 2.8.

The isolation of **9b** directly from a catalytic solution strongly supports the suggestion that palladium(0)-olefin complexes are indeed the resting state of the catalytic cycle. Since these complexes are also quite air sensitive, especially when in solution, the high oxygen sensitivity of the reaction is also explained. Since the amount of **9b** isolated in the crystalline state from the catalytic reaction was not sufficient for any further characterization, it was independently synthesized by the same procedure described in Scheme 13 for **9a**. The complex was isolated in 95% yield and characterized by elemental analysis and NMR spectroscopy. The ^{1}H NMR shows broad signals in the aromatic region, due to a dynamic rotation of the metal-olefin bond. As previously reported for the Pd(Phen)(dba) analogue [136] and for related complexes with PPh_3 as ancillary ligands and cinnamates as the olefins [139], the signals related to phenanthroline protons are broadened at 300 K. The olefin signals at 5.33 and 5.26 ppm are resolved even at room temperature, although the resolution improves at lower temperature. The $^3J_{HH}$ coupling constant of the olefinic protons decreases from 15.7 Hz of the free olefin to about 10 Hz, indicating a partial sp^3 character of the double bond as expected for an η^2-olefin complex. Upon decreasing the temperature to 203 K, the signals related to phenanthroline are better resolved, although signals related to the free olefin are also detected, indicating limited stability of the complex in solution. Indeed, the ^{1}H NMR spectrum recorded after the variable-temperature experiments showed broader signals also for the olefin protons indicating an exchange between the coordinated olefin and the free olefin in solution. As a comparison, complex **9a** showed a much lower stability in solution leading to color change within seconds, in the absence of an excess of the olefin. Therefore, it was not possible to record a ^{1}H NMR spectrum of the pure compound. However, in CD_2Cl_2 it was possible to assign to the complex a doublet at 5.12 ppm with a coupling constant of 10.4 Hz related to one of the olefinic protons (the signal related to the other proton overlapped with the solvent residual signal), as for **9b**, and broadened signals in the aromatic region related to phenanthroline protons.

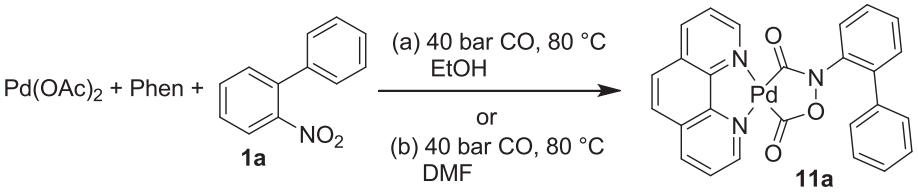
It should be remarked that the isolation and X-ray crystal structure characterization of **9a** and **9b** is itself noteworthy. Palladium(0) η^2-olefin complexes are in general little stable. Complexes with nitrogen ligands are only stable when the olefin bears electron-withdrawing groups, most often on both olefinic carbon atoms. Phenanthroline is not a good stabilizing ligand for these complexes and, to the best of our knowledge, only seven of them have been isolated with this ligand [132–138,140], only one of which was structurally characterized [140].

In Scheme 11, we have also addressed that even the reductive cyclization of β-nitrostyrenes by the same Pd/Phen catalytic system and CO as reductant is a very air sensitive reaction. Although we have not experimentally reinvestigated this reaction at the moment, we recall that several complexes of the type Pd(2,9-Me_2,4,7-Ph_2-Phen)(η^2-Ar-CH=C(H)NO_2) have been reported and three of them have been structurally characterized [141]. Since the nitro group is more electron-withdrawing than the ester and keto groups present in **8a** and **8b**, it appears likely that olefin complexes are formed even during the cyclization reactions of β-nitrostyrenes. In accord with the air sensitivity of the latter reactions, it may be noted that the structurally characterized β-nitrostyrene complexes were reported to be air sensitive even as single crystals, indicating that they should be much more so when in solution.

Concerning the resting state of the catalytic system when the cyclization of *o*-nitrobiphenyls is performed, any proposal should be consistent with the presence of the *o*-nitrosobiphenyl moiety in the complex. However, nitrosoarene palladium complexes are very reactive and still unprecedented with phenanthroline ligands. In the literature, very stable metallacycles of type **11** (see Scheme 16) have been obtained by reaction of nitrobenzene or related molecules with palladium acetate and phenanthroline under the influence of CO [142–145]. To test if an analogous metallacycle could be obtained starting from **3a**, the originally reported recipe for the synthesis of these metallacycles was performed (Scheme 16 (a)). Compound **11a** was indeed obtained, but, the solvent, ethanol, is quite different from that employed under our cyclization protocol, DMF. We thus repeated the reaction in this latter solvent



Scheme 15. Isolation of **9b** from a catalytic reductive cyclization of an *o*-nitrostyrene to the corresponding indole.



Scheme 16. Synthesis of **11a.**

(Scheme 16 (b)) and the same metallacycle was obtained, supporting the view that it can be formed and accumulated under the reaction conditions.

Complex **11a** is very stable and does not react at moderate temperatures. However, heating it in DMF at 170 °C, the typical reaction temperature, under 10 bar CO resulted in the formation of carbazole **2a**, but accompanied by a larger amount of the corresponding aniline, **4a** (Scheme 17 (a)). Interestingly, if the same base employed in the catalytic reactions, Na_3PO_4, was present, the relative amount of **2a** with respect to **4a** doubled (Scheme 17 (b)). This is in accord with the positive effect of bases in the cyclization of **3a** to **7a**.

Unfortunately, we could not isolate **11a** directly from a catalytic reaction mixture as we had done for **9b**. When high catalyst loadings were employed in order to increase the amount of metal complex, palladium black was invariably obtained. However, the fact that **11a** is formed in high yields in the same solvent as that employed in the catalytic reactions supports the view that it can form even under the typical reaction conditions and its stability is in agreement with the idea that it may represent the resting state of the catalyst.

It should be noted that we recently proposed the analogous metallacycle derived from nitrobenzene as an intermediate in its carbonylation to phenyl isocyanate [146]. However, the latter reaction requires the presence of an acid to proceed, whereas the synthesis of carbazoles proceeds in the presence of bases. Since we have shown that the cyclization reaction proceeds through the intermediate formation of nitrosoarenes, it is useful to draw some parallels with related reactions. It has long been known that when the reductive carbonylation reaction of nitrosoarenes is performed with different catalysts, azo- and azoxyarenes are the main products [69,147], even under conditions where carbonylated products, typically carbamates, are prevalently formed when nitroarenes are employed under the same experimental conditions. Quite importantly, it has been proved that when Pd/Phen catalytic systems are employed in carbonylation reactions of nitroarenes to carbamates, diarylureas or isocyanates, the addition of bases favors the formation azoxy- and azoarenes [148], whereas the addition of acids inhibits the formation of the latter and orients the reaction towards the formation of the carbonylated products [130,146,148–151]. The effect of acids and bases on the reactivity of **11a** is thus fully in line with what previously known for the reactivity of nitroarenes with Pd/Phen catalytic systems under CO pressure.

*2.8. Crystal structure of **9a** and **9b***

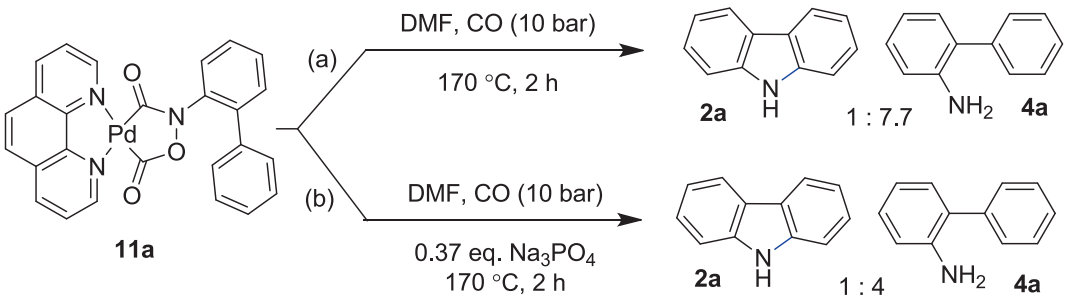
The samples of both species were of low quality due to their lamellar morphology and the easy delamination. For **9b** this prevented the possibility to cool down the crystals as they easily broke. Nevertheless, the ambient temperature data collection was sufficient to obtain a good structure determination. For **9a**, instead, a low temperature data collection could be carried out but all samples tested were affected by severe twinning. Therefore, for this species the structure refinement is extremely complicated and we could obtain only information on the configuration of the complex and the conformation of the ligands (Fig. 7).

Both compounds crystallize in the monoclinic system ($P2_1/n$ and $C2/c$ space groups for **9a** and **9b** respectively). The molecules form columns stacking the phenanthroline ligands that coordinate the Pd atom through the N atoms. The nitroarene ligands are side-on coordinated to the metal through the central double bond and therefore their plane is perpendicular to that of the phenanthroline. In both compounds, each molecule is approximately 90° rotated compared to the two vicinal molecules along the column, forming a sort of 4-fold helix (without any exact 4_1 axis, obviously). In **9a**, this implies two molecules in the asymmetric unit, whereas in **9b**, the C-centered type of lattice implies only one molecule in the asymmetric unit. The other difference is that in **9a**, the columns are parallel to the monoclinic b axis, whereas in **9b**, they are perpendicular to b and parallel to the c axis.

In the literature, crystallographically characterized Pd(0) olefin complexes with phenanthroline or its derivatives as ligands are very rare. Only Zagorodnikov *et al.* [140] reported a Pd-phenanthroline complex with a coordinated tetracyano-ethylene. In the only other crystallographically characterized complexes, the ligand was bathocuproine [141,152,153], where the presence of two methyl groups in both positions *ortho* to the nitrogen atoms helps stabilizing the compounds. A few more structures are known of Pd-bipyridine complexes [154,155].

3. Conclusions

Our mechanistic study of the mechanism of the heterocyclization reactions of nitroarenes when carbon monoxide is used as a reductant and transition metal complexes, with a focus on the palladium/phenanthroline system, are employed as catalysts involved many different types of approaches: from competitive and trapping experiments in



Scheme 17. Reactivity of **11a** under CO pressure.

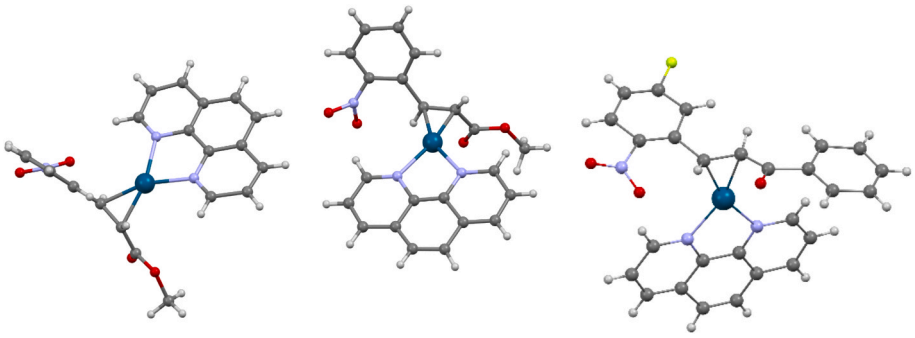


Fig. 7. Ball and sticks models of the molecular structures of **9a** (left) and **9b** (right) obtained from single crystal X-ray diffraction. For **9a**, there are two molecules in the asymmetric unit (both shown in the picture).

catalytic reactions, to kinetic investigations, theoretical calculations, the isolation and single crystal X-ray structure determination of palladium-containing reaction intermediates and the study of their reactivity. Data previously reported in the literature were also considered in a critical way and reinvestigated if necessary. In particular, the previously reported evidence in favor of the formation of metal-imido intermediates was dismissed. Overall, strong evidence was gained that the C-N bond formation occurs after the nitro group has been reduced to nitroso and before any further reduction takes place. The cyclization step almost surely occurs outside the coordination sphere of the metal during the formation of carbazoles and oxazines, but the same likely occurs during the formation of other *N*-heterocycles by analogous reactions. The reason for the different air-sensitivity of the carbazole and indole syntheses was identified in the different oxidation state of palladium in the resting state of the catalytic cycle: Pd(II) for carbazoles and Pd(0) for indoles. As a sort of "side product" of the theoretical investigation of the cyclization of *o*-nitrosobiphenyl to *N*-hydroxy-carbazole, an unprecedented role for DMF was found, adding to the "not just as a solvent" roles that had already been identified [97].

4. Experimental

4.1. Materials and general procedures

Unless otherwise stated, all reactions and manipulations were performed under a dinitrogen atmosphere using standard Schlenk and cannula techniques. All glassware and magnetic stirring bars were dried in an oven at 120 °C for at least two hours and allowed to cool under vacuum prior to use. CH_3CN was dried by distillation over CaH_2. DMF was dried by distillation over CaH_2 under reduced pressure at 60 °C. Acetone was degassed and dried over activated 4 Å molecular sieves. Hexane and diethyl ether were distilled from sodium/benzophenone ketyl. Methanol was distilled from $Mg(OCH_3)_2$. All solvents were stored under dinitrogen after the drying procedure described above. Phenyl formate (HCOOPh) was prepared following a literature procedure [38], degassed, and stored under dinitrogen. Deuterated solvents were purchased from Sigma-Aldrich. DMSO–d_6, $PhNO_2$-d_5 and CD_2Cl_2 were used as received, whereas $CDCl_3$ was filtered through basic alumina and stored under dinitrogen over activated 4 Å molecular sieves. 1,10-Phenanthroline (Phen) was purchased as the hydrate (Sigma-Aldrich). Prior to use, it was dissolved in CH_2Cl_2, dried over anhydrous Na_2SO_4, and the obtained solution was filtered under dinitrogen, and evaporated to dryness *in vacuo*. The anhydrous Phen was weighed in the air, but stored under dinitrogen to prevent moisture uptake. Triethyl amine (Et_3N) was distilled from CaH_2 and then stored under dinitrogen. Sodium phosphate (Na_3PO_4) was dried by heating at 180 °C under vacuum for 8 h. It was weighed in the air but stored under dinitrogen to avoid reabsorption of water. All palladium precursors $(Pd(OAc)_2$ [156]; $Pd(CH_3CN)_2Cl_2$ [157]; and $Na_2[PdCl_4]$ [158]) used in this study were synthesized from commercially available $PdCl_2$ following established literature procedures. Cyclohexene was distilled over sodium and stored under dinitrogen. All other reagents were purchased from Sigma-Aldrich or TCI Europe NV and used without further purification. All organic compounds whose synthesis is not mentioned in the following are commercial products and were employed as received. Flash column chromatography was carried out on Macherey-Nagel silica gel (0.04–0.063 mm). ^1H NMR and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance DRX 400 or Bruker Avance NEO 400 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS). Gas chromatographic analyses were performed on a Shimadzu 2010 gas chromatograph equipped with a Supelco SLB™-5 ms capillary column, employing biphenyl as an internal standard. GC–MS analyses were performed on an Agilent Technologies 7890A gas-chromatograph, equipped with a 5975c INER MSD mass detector. Elemental analyses (C, H, N) were performed on a PerkinElmer 2400 CHN elemental analyzer.

4.2. Kinetic studies

Kinetic studies of the thermal cyclization reaction of **3a** were investigated by monitoring substrate consumption using UV spectrophotometry. A single beam UV–visible spectrophotometer (Agilent 8453) was used, and the absorbance measurements were obtained at 770 nm (the λ_{max} of **3a**). Reactions were conducted under a nitrogen atmosphere in a Schlenk glassware (see Fig. S1) composed of a 10 mL reaction chamber connected to a glass cuvette, allowing the reaction progress to be followed without transferring the reaction content into an external cuvette. Before initiating the reaction, 5 mL of DMF was transferred into the apparatus under nitrogen and the blank was recorded. Then, the solvent was discarded, and the apparatus cleaned. Subsequently, the apparatus was evacuated and filled with dinitrogen three times and 1 mL of *o*-nitrosobiphenyl stock solution (10 mg, 0.055 mmol; prepared by dissolving 100 mg of **3a** in 10 mL DMF) was added in a dinitrogen stream using a pipette. For experiments performed in the presence of Et_3N or other additives, the required amount of additive relative to **3a** was added at this stage. Additional DMF was added to reach a total volume of 5 mL, and then the initial absorbance (time = 0) was recorded. The reaction mixture was then heated to 100 °C by placing the 10 mL chamber of the apparatus in a preheated oil bath. At selected time intervals, the reaction mixture was rapidly cooled in a water bath, and the absorbance measured. Reaction time count was stopped when the chamber was removed from heating and started again when it was inserted again in the oil bath.

4.3. Synthesis of 4,4′-dimethoxy-2-nitro-1,1′-biphenyl (**1c**)

Compound **1c** was prepared following a previously reported procedure [35]. In an oven-dried 50 mL Schlenk flask, 1-bromo-4-methoxy-2-nitrobenzene (10 mmol, 1.0 equiv.), (4-methoxyphenyl)boronic acid (11 mmol, 1.1 equiv.), potassium carbonate (20 mmol, 2.0 equiv.), and

tetrakis(triphenylphosphine)palladium(0) (0.1 mmol, 0.01 equiv.) were dissolved in a mixture of water (10 mL) and toluene (15 mL); then the reaction mixture was stirred under reflux. After completion of the reaction (12 h), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the dry solution was filtered and evaporated to dryness under reduced pressure. Crystallization from methanol afforded compound **1c** as yellow crystals (2.42 g, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.21 (d, J = 8.7 Hz, 2H), 7.13 (dd, J = 8.6, 2.6 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 158.9, 149.8, 132.9, 129.6, 129.3, 128.3, 118.7, 114.3, 109.0, 56.0, 55.4 ppm. Anal. calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40; Found: C, 64.47; H, 5.05; N, 5.25.

4.4. General procedure for the synthesis of *4a* and *4c*

Compounds **4a** and **4c** were synthesized according to a modification of a previously reported procedure [159]. In a 50 mL Schlenk flask, the appropriate *o*-nitrobiphenyl derivative (2.5 mmol, 1.0 equiv.) and tin(II) chloride dihydrate (15 mmol, 6.0 equiv.) were dissolved in ethanol (20 mL). The reaction mixture was stirred under reflux, and progress was monitored by TLC until the reaction was complete. The mixture was neutralized by the addition of a saturated aqueous sodium bicarbonate solution and then extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed sequentially with a saturated sodium bicarbonate solution (3 × 15 mL) and water (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure to afford the corresponding *o*-aminobiphenyl derivative.

*2-Amino-1,1′-biphenyl (**4a**)*: Obtained as a light brown solid (351 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.42 (m, 4H), 7.41–7.32 (m, 1H), 7.23–7.10 (m, 2H), 6.86 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 3.83 (br. s, 2H, NH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.35, 139.55, 130.58, 129.21, 128.93, 128.61, 127.88, 127.30, 118.93, 115.85 ppm. Anal. calcd. for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28; Found: C, 84.80; H, 6.66; N, 8.18.

*4,4′-Dimethoxy-[1,1′-biphenyl]-2-amine (**4c**)*: Obtained as a yellow solid (430 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.7 Hz, 2H), 6.39 (dd, J = 8.4, 2.5 Hz, 1H), 6.32 (d, J = 2.5 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.75 (br. s, 2H, NH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 158.7, 144.9, 131.7, 131.4, 130.4, 120.7, 114.3, 104.3, 101.2, 55.5, 55.3 ppm. Anal. calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11; Found: C, 72.67; H, 6.72; N, 6.15.

4.5. General procedure for the synthesis of *3a* and *3c*

Compounds **3a** and **3c** were prepared following a previously reported procedure [160]. In a 25 mL Schlenk flask, the appropriate *o*-aminobiphenyl derivative (2 mmol, 1.0 equiv.) was dissolved in dichloromethane (5 mL). To this solution, Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, 10 mmol, 5.0 equiv.) and water (20 mL) were added. The biphasic reaction mixture was stirred under a dinitrogen atmosphere at room temperature, and the progress was monitored by TLC until the reaction was complete (8 h). The layers were separated, and the aqueous one was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed sequentially with 1 N HCl (2 × 15 mL), saturated $NaHCO_3$ solution (3 × 15 mL), water (3 × 15 mL), and brine (2 × 15 mL), then dried over anhydrous Na_2SO_4. The mixture was filtered, and the solvent was removed under reduced pressure. The crude product was purified by recrystallization from ethanol or by column chromatography to afford the corresponding *o*-nitrosobiphenyl derivative. In case of **3a**, the NMR was concentration dependent due to dimerization of *o*-nitrosobiphenyls in solution [161].

*2-Nitroso-1,1′-biphenyl (**3a**)*: Obtained as white crystals (205 mg, 56% yield) after recrystallization from ethanol. In the following ^{1}H NMR, a doublet at 5.61 (integration = 0.47) corresponds to two aromatic protons arising from the dimer while that at 6.24 (integration = 1.0) is due to one aromatic proton in the monomer [161]. Thus, the ratio of monomer to dimer in that solution was almost 4 to 1, although the compound is only present as a dimer in the solid state. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00–7.84 (m, 4H, **dimer**), 7.75–7.61 (m, 5H, **dimer**), 7.60–7.49 (m, 7H, 5H **monomer** + 2H **dimer**), 7.48–7.39 (m, 2H, **monomer**), 7.34 (d, J = 6.7 Hz, 2H, **dimer**), 7.22–7.12 (m, 1H, **monomer**), 7.06 (t, J = 8.2 Hz, 2H, **dimer**), 6.90 (d, J = 7.9 Hz, 1H, **dimer**), 6.24 (d, J = 8.0 Hz,1H, **monomer**), 5.61 (d, J = 7.8 Hz, 2H, **dimer**) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4, 145.6, 139.9, 139.4, 137.0, 136.8, 136.6, 136.4, 135.9, 134.7, 132.4, 131.9, 131.6, 131.4, 130.5, 129.9, 129.2, 129.2, 128.9, 128.6, 128.4, 128.3, 128.3, 128.1, 128.0, 127.8, 125.1, 123.5, 105.6 ppm. Anal. calcd. for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65; Found: C, 78.98; H, 5.0; N, 7.80.

*4,4′-Dimethoxy-2-nitroso-1,1′-biphenyl (**3c**)*: Obtained as yellow solid (228 mg, 47%) after column chromatography using hexane/ethyl acetate (9:1 to 8:2) as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.36 (dd, J = 8.6, 2.7 Hz, 1H), 7.04 (d, J = 8.6 Hz, 2H), 5.75 (d, J = 2.7 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 160.0, 158.7, 140.1, 133.3, 133.0, 129.4, 124.2, 113.9, 89.0, 55.7, 55.5 ppm. Anal. calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76; Found: C 68.78; H 5.53; N 5.65.

4.6. Synthesis of (Z)-1,2-di([1,1′-biphenyl]-2-yl)diazene oxide (*5a*)

Compound **5a** was prepared by reductive dimerization of **3a** according to a modified previously reported procedure [162]. In a 23 mL heavy-walled glass pressure tube (Duran®) equipped with a magnetic stirring bar, compound **3a** (1 mmol) was placed. The tube was transferred to a wide-mouth Schlenk tube and subjected to three evacuation-backfill cycles with dinitrogen to remove air. Isopropanol (5 mL) was then added, and the tube was sealed with a Schott screw cap equipped with a PTFE-protected seal. The sealed tube was placed in a preheated aluminum block at 100 °C and stirred for 16 h. At the end of the allotted time, the pressure tube was removed from the aluminum block and allowed to cool to room temperature. Upon reaching room temperature, yellow crystals of **5a** began to precipitate. The crystals were collected by filtration, washed with cold isopropanol and hexane, and air-dried to afford the desired product (53 mg, 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.26 (m, 17H), 7.16 (dd, J = 5.9, 3.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 142.0, 139.5, 137.8, 137.1, 135.5, 131.1, 130.5, 130.1, 129.0, 128.7, 128.4, 128.2, 128.1, 127.8, 127.5, 123.4, 121.4 ppm. Anal. calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28; Found: C 81.08; H 7.35; N 5.25.

4.7. Synthesis of 2,7-dimethoxy-9H-carbazol-9-ol (*7c*)

In an oven-dried 10 mL Schlenk flask, compound **3c** (0.2 mmol) was dissolved in DMF (5 mL) and stirred at 100 °C under a dinitrogen atmosphere. It is worth noting that **3c** exhibits poor solubility in DMF at room temperature; therefore, heating to 100 °C was essential not only to promote the reaction but also to ensure complete dissolution of the starting material. The progress of the reaction was monitored by TLC until completion. Upon completion, the solution was already not completely clear at 100 °C and the product started to precipitate upon cooling to RT. DMF was removed under reduced pressure at 60 °C, affording **7c** as the sole product (48 mg, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.87 (d, J = 8.5 Hz, 2H), 6.94 (s, 2H), 6.75 (d, J = 7.1 Hz, 2H), 3.85 (s, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.9, 140.1, 120.3, 112.4, 107.7, 91.9, 55.3 ppm. Anal. calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76; Found: C 68.73; H 5.56; N 5.77.

4.8. Competitive reactions

To avoid weighing errors associated with small quantities of the palladium catalyst, stock solutions of $Na_2[PdCl_4]$ and Phen in DMF were prepared and stored under dinitrogen. **1b** (0.27 mmol, 0.5 equiv.) and either **3a**, **4a**, or **5a** (0.27 mmol, 0.5 equiv.) were weighed in the air and transferred to a 23 mL heavy-walled glass pressure tube (Duran®) equipped with a magnetic stirring bar. The tube was placed inside a wide-mouth Schlenk flask and subjected to three evacuation-backfill cycles with dinitrogen to remove air. The required volumes of the catalyst (1 mol%) and ligand (5 mol%) stock solutions were then added, and the mixture was stirred for 10 min to allow formation of the Pd/phenanthroline complex. Subsequently, Na_3PO_4 (0.073 mmol, 0.135 equiv.) was added without stirring, followed by additional DMF to reach a total volume of 10 mL. HCOOPh (2.38 mmol, 4.4 equiv.) was then introduced, and the pressure tube was sealed with a Schott screw cap equipped with a PTFE-protected seal. The tube was placed in a custom-made aluminum block preheated to 170 °C and stirred for 5 h. At the end of the reaction, the pressure tube was removed from the oil bath and allowed to cool to room temperature. The screw cap was carefully removed in a fume hood, and excess carbon monoxide was allowed to vent. (Caution: Dissolved CO may continue to evolve from the solution for several minutes; ensure adequate ventilation.) Biphenyl was added as an internal standard and the reaction mixture was analyzed by GC. Results are reported in paragraph 2.3.

4.9. In situ trapping of **3a** by [4 + 2] cycloaddition with 2,3-dimethylbutadiene

The reaction was performed similarly to the competitive experiments described above, but only **1a** (0.54 mmol, 1.0 equiv.) was employed as a nitrogen-containing reagent and 2,3-dimethylbutadiene (2.16 mmol, 4.0 equiv.) was also added with sodium phosphate. The reaction was run at 140 °C for 24 h. GC analysis showed the presence of unreacted **1a**, but no carbazole **2a** was detected. The remaining DMF was removed under reduced pressure. The crude residue was subjected to column chromatography on silica gel using hexane/ethyl acetate (9:1 + 1% Et_3N) as the eluent. 2-([1,1′-biphenyl]-2-yl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine **(6a)** was delivered exclusively from the trapping reaction as a colorless solid. No carbazole **2a** was detected either during the GC analysis or as a result of the chromatographic purification. Results are reported in paragraph 2.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.5 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.35 – 7.32 (m, 1H), 7.30 (d, J = 7.4 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.18 (t, J = 7.3 Hz, 1H), 3.97 (s, 2H), 3.32 (s, 2H), 1.53 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 141.1, 135.2, 131.1, 129.0, 128.2, 128.1, 126.7, 124.8, 124.5, 122.8, 117.7, 72.1, 56.5, 15.9, 13.7 ppm. Anal. calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28; Found: C 81.16; H 7.35; N 5.25.

4.10. Synthesis of **9a**

In an oven-dried Schlenk tube, $Pd(dba)_2$ (0.35 mmol, 1 equiv.) was dissolved in 10 mL of dry acetone. The solution was then filtered through a pad of Celite to ensure the absence of any Pd-black impurities. The filtrate was added to a solution of Phen (0.70 mmol, 2 equiv.) in 5 mL of dry acetone and stirred for 30 min to allow formation a suspension of the orange complex Pd(Phen)(dba). A solution of **8a** (0.70 mmol, 2 equiv.) in 5 mL of dry acetone was then added gradually to the Pd(Phen)(dba) solution. An immediate color change to wine red was observed upon addition of **8a** and the suspension turned into a clear solution. The mixture was stirred for 45 min, after which 30 mL of dry distilled hexane was added to precipitate **9a**. The mixture was transferred to a centrifuge tube under nitrogen and centrifuged at 3500 rpm for 10 min. The mother liquor was carefully removed, and the red powder was washed with hexane (3 × 5 mL), with centrifugation after each wash. The resulting red powder was collected under nitrogen, dried under vacuum, and stored under nitrogen for further experiments. The product was obtained as a red powder (143 mg, 83% yield). Anal. calcd. for $C_{22}H_{17}N_3O_4Pd$: C, 53.51; H, 3.47; N, 8.51. Found C, 53.75; H, 3.60; N, 8.31.

4.11. Reaction of **9a** with CO

In an oven-dried Schlenk tube under dinitrogen, **9a** (0.04 mmol, 1 equiv.) was dissolved in 3 mL of CH_3CN. The solution was quickly heated to 80 °C and CO was allowed to enter the tube. After 5 min the CO flow was stopped, the Schlenk tube was carefully sealed, and the atmosphere was exchanged back to nitrogen. The reaction mixture was then analyzed by GC.

4.12. Isolation of **9b** from the reductive cyclization reaction of 5-fluoro-2-nitrochalcone

A heavy-walled glass pressure tube (Duran®) equipped with a magnetic stirring bar was charged with 5-fluoro-2-nitrochalcone, **8b** (0.3 mmol, 1.0 equiv.), and Phen (0.1 mmol, 0.33 equiv.). The pressure tube was then placed inside a wide-mouth Schlenk tube, and the assembly was subjected to three evacuation-backfill cycles with dinitrogen to remove air. Under a positive flow of dinitrogen, dry CH_3CN (5 mL) was added to dissolve the solids, followed by $Pd(CH_3CN)_2Cl_2$ (0.05 mmol, 0.17 equiv.), and the mixture was stirred for 10 min to allow coordination of Phen to palladium. Subsequently, HCOOPh (1.8 mmol, 6.0 equiv.), additional CH_3CN (4 mL), and DMF (1 mL) were added (total solvent volume = 10 mL). Finally, Et_3N (50 μL) was introduced. The pressure tube was then promptly sealed with a PTFE-lined screw cap - while still under dinitrogen inside the Schlenk tube, then removed and stirred in a preheated aluminum block at 100 °C for 45 min. At the end of the reaction, the pressure tube was removed from the heating block and immediately immersed in a cold-water bath to ensure rapid quenching. The pressure tube was then placed inside a wide-mouth Schlenk tube under a continuous flow of dinitrogen, and the screw cap was carefully removed in a fume hood to vent excess carbon monoxide. (Caution: Dissolved CO may continue to evolve; ensure adequate ventilation.) The mixture was filtered through a pad of Celite under a dinitrogen atmosphere to remove any palladium black that may have formed during the early stages of the reaction. The filtrate was evaporated *in vacuo* and the residue was redissolved in dry, degassed acetone (5 mL) inside a Schlenk tube under dinitrogen. The solution was cooled to −78 °C using a dry ice/acetone bath. This cold solution was then carefully layered with distilled hexane (15 mL) and allowed to stand at room temperature until full diffusion occurred, affording crystals of the **9b** suitable for a single-crystal X-ray diffraction analysis.

4.13. Independent synthesis of **9b**

In an oven-dried Schlenk tube, $Pd(dba)_2$ (0.040 mmol, 1 equiv.) and Phen (0.080 mmol, 2 equiv.) were dissolved in 10 mL of dry acetone. The solution was stirred at RT for 1 h to allow formation a suspension of the orange complex Pd(Phen)(dba). A solution of **8b** (0.242 mmol, 6 equiv.) in 2 mL of dry acetone was then added gradually to the Pd(Phen)(dba) solution. An immediate color change to wine red was observed upon addition of **8b** and the suspension turned to a clear solution. The mixture was stirred for 1 h, during which time a red solid started to precipitate. The solution was concentrated to about 1/3 vol under vacuum, after which 30 mL of dry distilled Et_2O was added to precipitate **9b**. The mixture was transferred to a centrifuge tube under nitrogen and centrifuged at 3500 rpm for 10 min. The mother liquor was carefully removed, and the red powder was washed with Et_2O (2 × 5 mL), with centrifugation after each wash. 21 mg, 95% yield. Anal. calcd. for $C_{27}H_{18}FN_3O_3Pd$: C, 58.13; H, 3.25; N, 7.53. Found C, 57.76; H, 3.12; N, 7.32. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.74 (br s, 1H), 8.32 (br m, 2H), 8.24 (d, J = 6.9 Hz, 2H), 8.01 (br s, 1H), 7.90 – 7.77 (m, 3H), 7.660 – 7.53 (m,

4H), 7.43 (d, $J = 9.1$ Hz, 2H), 6.83 (t, $J = 6.9$ Hz, 1H), 5.34 (d, overlapped with residual solvent signal, 1H, vinyl), 5.28 (d, $J = 9.9$ Hz, 1H, vinyl).

4.14. Synthesis of **11a**

Complex **11a** was prepared by adapting a previously reported procedure [143]. $Pd(OAc)_2$ (0.45 mmol, 1 equiv.) and Phen (1.35 mmol, 3 equiv.) were placed in a 50 mL glass liner. The liner was placed inside a wide-mouth Schlenk tube, and the assembly was subjected to three evacuation-backfill cycles with dinitrogen to remove air. 5 mL of ethanol was added and the solution was left under stirring for 15 min. to allow the *in-situ* formation of Pd(Phen)(OAc). 2-Nitro-1,1′-biphenyl (18 mmol, 40 equiv.) was then added, followed by additional 5 mL of ethanol. The liner was closed with a screwcap having a glass wool-filled open mouth which allows gaseous reagents to exchange. It was then transferred to a 200 mL stainless steel autoclave with magnetic stirring while flushing the latter with dinitrogen. The autoclave was then charged with 40 bar CO and discharged three times before being finally charged with 40 bar CO at room temperature. The autoclave was inserted in an aluminum block preheated to 80 °C and heated under stirring for 2.5 h. At the end of the reaction, the autoclave was cooled with an ice bath and vented in a fume hood. The pale-yellow solid that formed was separated by filtration and then washed several times with ethanol and diethyl ether to afford **11a** (216 mg, 86% yield). ^{1}H NMR (400 MHz, $C_6D_5NO_2$) δ 10.14 (d, $J = 4.7$ Hz, 1H), 10.03 (d, $J = 4.6$ Hz, 1H), 8.62 (d, $J = 8.0$ Hz, 1H), 8.58 (d, $J = 8.0$ Hz, 1H), 8.01 (s, 2H), 8.00 – 7.90 (m, 4H), 7.89 – 7.84 (m, 1H), 7.69 – 7.61 (m, 3H), 7.58 (m, overlapped with residual solvent signal), 7.43 (t, $J = 7.4$ Hz, 1H). ^{13}C NMR (101 MHz, $C_6D_5NO_2$) δ 191.4 (*C*O), 188.5 (*C*O), 151.7 (*C*H, Phen), 151.5 (*C*H, Phen), 145.9 (*C*), 145.5 (*C*), 142.6 (*C*), 140.5 (*C*), 139.2 (2 × *C*H, Phen), 138.4(*C*), 131.3 (*C*H), 130.9 (*C*H), 130.0 (2 × *C*H), 129.1 (*C*H, overlapped with $C_6D_5NO_2$ signal) 128.9 (CH), 128.7 (2 × *C*H), 128.5 (*C*), 127.9 (*C*H), 127.5 (*C*H), 127.45 (*C*H), 125.4 (*C*H), 125.3 (*C*H). Due to the very low solubility and the strong signals of the deuterated solvent, one of the quaternary carbons was not detected, likely due to overlapping with solvent signals. Anal. calcd for $C_{26}H_{17}N_3O_3Pd$: C, 59.39; H, 3.26; N, 7.99; Found: C 59.00; H 3.47; N 7.94.

The same reaction was repeated by employing DMF as the solvent. In this case, methanol (15 mL) was added to the reaction solution at the end of the reaction to complete the precipitation of the product. The latter was separated by filtration, washed with methanol (2 × 5 mL) and dried *in vacuo*. The product was confirmed to be **11a** by the identity of its X-ray powder diffraction spectrum with that of the compound prepared in ethanol. Due to the very poor solubility of **11a** in all solvents, this technique was deemed more suitable to prove the identity of the products obtained in the two solvents.

4.15. Reaction of **11a** under CO pressure

A 4 mL glass vial equipped with a magnetic stirring bar was charged with **11a** (0.05 mmol, 1.0 equiv.). For the experiment requiring a base, Na_3PO_4 (0.02 mmol, 0.37 equiv.) was also added. The vial was then placed in a custom-made copper block inside a wide-mouth Schlenk tube, and the assembly was subjected to three evacuation-backfill cycles with dinitrogen to remove air. Afterwards, DMF (1 mL) was added, and the vial was sealed with a screw cap fitted with a septum and a vent needle to allow gaseous reagent exchange. The sealed vial and the copper block were then placed inside a stainless-steel autoclave. The autoclave was purged by pressurizing and releasing carbon monoxide (5 bar) three times at room temperature. It was then pressurized with CO to 10 bar and placed in a preheated custom-made aluminum block at 170 °C with magnetic stirring for 2 h. At the end of the reaction, the autoclave was cooled in an ice bath to ensure rapid quenching and carefully depressurized in a fume hood. The reaction mixture was then analyzed by GC using biphenyl as an internal standard.

4.16. Formation of N-(cyclohex-2-en-1-yl)aniline during a reaction of $PhNO_2$ with cyclohexene

Similarly to the published procedure, $Pd(OAc)_2$ (0.05 mmol) and DPPP (0.075 mmol) were weighed in a 50 mL glass liner equipped with a magnetic stirring bar. The liner was then placed in a Schlenk tube with a wide mouth and evacuated and backfilled with dinitrogen three times. Then dry methanol (25 mL) and dry cyclohexene (5 mL) were added and the solution stirred for 15 min to allow coordination of the ligand to palladium. $PhNO_2$ (2.50 mL, 24.4 mmol) was then added. The liner was closed with a screwcap having a glass wool-filled open mouth that allows gaseous reagents to exchange and transferred to a 200 mL stainless steel autoclave with magnetic stirring while flushing the latter with dinitrogen. The autoclave was then charged with 40 bar CO and discharged three times before being finally charged with 50 bar CO at room temperature. The autoclave was inserted in an aluminum block preheated to 110 °C and heated under stirring for 4.5 h. At the end of the reaction, the autoclave was cooled with an ice bath and vented in a fume hood. The solution was analyzed by GC–MS. Apart from the main peaks due to unreacted nitrobenzene and produced methyl phenylcarbamate and azoxybenzene, a lower intensity peak was observed showing a parent mass peak at $m/z = 173$ and a fragmentation pattern (Fig. S2) closely matching that reported in Fig. 2 of ref. [116]. A solution containing *N*-(cyclohex-2-en-1-yl)aniline was then prepared by performing the allylic amination of nitrobenzene with cyclohexene employing $Ru_3(CO)_{12}$ as catalyst, in the presence of Tol-BIAN (Tol-BIAN = bis-(tolylimino)acenaphthene) according to the procedure already reported by us [13]. The solution was analyzed by the same method and a strong peak was observed at the same retention time as that observed in the previous reaction and with an identical fragmentation pattern (Fig. S3).

4.17. Computational details

All calculations were carried out using Density Functional Theory (DFT) as implemented in Gaussian 16 [163]. Geometry optimizations were conducted at the PBE0/6-311G(d,p) [164,165] level of theory, using frequency analyses to characterize intermediates and transition-states. All minimum energy intermediates were confirmed by the absence of imaginary frequencies, and the transition states were verified by the presence of a single imaginary frequency. Transition states were located using a Potential Energy Surface scan. Intrinsic reaction coordinate (IRC) [166] calculations were performed to assign connectivity with preceding and following minima. In some cases, the transition states were calculated using the quadratic synchronous transit (QST3) method [167], which requires only an initial guess for the transition-state. Single-Point energy calculations were carried out using the M06 functional [168] in combination with the 6–311++G(d,p) [165,169] basis set, including Grimme's D3 empirical dispersion correction (GD3) [170]. Solvent effect was taken into account implicitly using the Polarizable Continuum Model (PCM) [171], with *N,N*-dimethylformamide (DMF) as the solvent. Overall, this protocol can be denoted as: M06-GD3/6–311++G(d,p) (PCM, solvent = DMF) // PBE0/6-311G(d,p).

4.18. Crystal structure determination

Single crystals of **9a** and **9b** were selected under a microscope, immersed in protective perfluoro-ether oil, and mounted on a goniometer head on a Rigaku XtaLAB Synergy, Dualflex diffractometer, equipped with Oxford Cryosystem 800 + cryostat, Hpyx-6000 hybrid pixel detector. X-ray diffraction was measured using microsource Cu-Kα radiation at T = 173 K for **9a** and ambient temperature for **9b** (due to crystal breaking on lowering the temperature). The structure was solved with ShelXT [172] using the intrinsic phasing solution method and Olex2 [173] as the graphical interface. The models were refined with olex2.refine 1.537 using Gauss-Newton minimization [174]. For **9b**, a

full structure refinement was possible, with all non-hydrogen atoms treated anisotropically and hydrogen atom positions calculated geometrically and refined using the riding model. For **9a**, only Pd was treated anisotropically and all other atoms are refined isotropically with H atoms at geometrically calculated positions. Because **9a** is severely twinned (with at least 5 distinct diffraction domains visible in the patters) the reflections used in the refinement were those obtained from the integration of the two most visible domains and excluding the overlapping reflections. For this reason, the overall completeness of the dataset is necessarily low. Moreover, the diffraction of this species is particularly scares and therefore many reflections were below the observation threshold. All other tested samples of **9a** showed similar features (twinning and scares diffraction) and no better data could be therefore collected for this species. Crystallographic tables are reported in the Supporting Information. Crystallographic data were deposited at the Cambridge Crystallographic Data Center, with deposition numbers CCDC-2560429-2560430.

CRediT authorship contribution statement

Manar Ahmed Fouad: Writing – review & editing, Investigation. **Doaa R. Ramadan:** Writing – review & editing, Investigation. **Francesco Ferretti:** Writing – review & editing, Supervision, Methodology, Investigation. **Artur Brotons Rufes:** Writing – review & editing, Writing – original draft, Investigation. **Simona Russo:** Writing – review & editing, Investigation. **Piero Macchi:** Writing – review & editing, Writing – original draft, Investigation. **Chiara Costabile:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Fabio Ragaini:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2026.117164. Kinetic, computational and crystallographic data, NMR and mass spectra, and details of the X-ray diffraction experiments.

Data availability

Relevant data have been included in the Supplementary Material. Crystallographic data were deposited at the Cambridge Crystallographic Data Center, with deposition numbers CCDC- 2560429-2560430.

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