Catalytic Reductive Cyclization of 2-Nitrobiphenyls Using Phenyl formate as CO Surrogate: a Robust Synthesis of 9*H*-Carbazoles

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

[a] *Dipartimento di Chimica, Università degli Studi di Milano, via C. Golgi 19, 20133, Milano (Italy)*

[b] *Chemistry Department, Faculty of Science, Alexandria University, P.O. Box 426, Alexandria, 21321, Egypt*

email: fabio.ragaini@unimi.it

Abstract

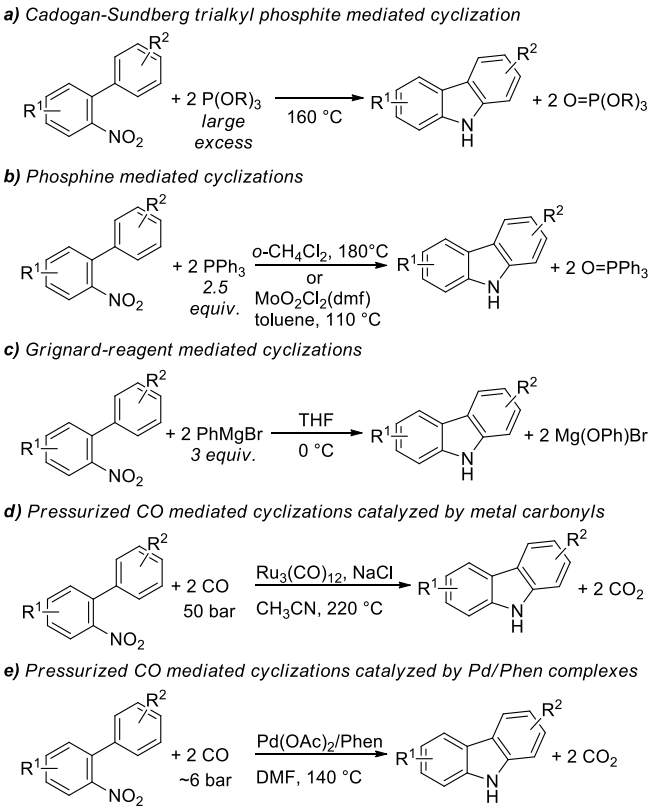
A palladium/phenanthroline catalyzed reductive cyclization of *o*-nitrobiphenyls to 9*H*-carbazoles operated by *in situ* released CO is described. In the present method, the presence of phenyl formate is essential to avoid the use of high-pressure equipment and allows to perform the reaction in a single thick-walled glass tube. The identity of the base, which catalyzes the formate decomposition, is crucial to the selectivity of the reaction. Stability of the catalyst is influenced by the presence of chloride anions. Carbazole yields are most often higher than those previously reported using pressurized CO. The optimized catalytic system features excellent stability and moisture and air tolerance allowing to perform the reaction with low catalyst loadings.

Keywords: 9*H*-carbazole - reductive cyclization – nitrobiphenyl – carbon monoxide surrogate – palladium – phenyl formate

1. Introduction

Carbazoles are a class of compounds that find application in many different industrial fields. Indeed, the carbazole scaffold is present in biologically active natural compounds and synthetic drugs [1-5]. Carbazoles are also valuable π-extended building blocks for the synthesis of small-molecules and polymers with opto/thermo-electronic applications [6]. Owing to the wide importance of *N*-heterocycles, the development of synthetic methods to their scaffold has been intensively studied in the past. However, the development of step-saving procedures with low

environmental impact is still of high importance. As for other classes of *N*-heterocycles, conventional low atom-economical syntheses are still widely used for carbazoles preparation both in academic and industrial laboratories. A convenient approach to access the *N*-heterocyclic scaffolds, and in particular the one of carbazoles, makes use of nitro compounds as starting materials and involves a C-H functionalization that allows for C-N bond formation without the need for highly functionalized substrates. In this context, the use of phosphorus (III) compounds as stoichiometric reductants (Scheme 1a,b), either employing Cadogan-Sundberg type [7-9] or metal-catalyzed protocols [10], is widely diffused despite the amounts of phosphorus wastes produced that rise environmental concern. More recently, a procedure in which small-ring phosphacycloalkane acts as an organocatalyst (20 mol%) and phenylsilane as the terminal reductant was described [11]. Methods employing stoichiometric organometallic reagents have been also reported (Scheme 1c) [12].



Scheme 1. Synthesis of carbazoles by reductive cyclization of 2-nitrobiphenyls.

Several transition metal catalyzed inter- and intramolecular cyclization reactions are among the most efficient methods to access *N*-heterocyclic scaffolds [13-19]. Against this background, the catalytic deoxygenative cyclization of *ortho*-substituted nitro compounds to heterocycles using CO as the reductant is among the most efficient and versatile methods [20-24]. The reaction has the

great advantage of producing only CO_2 as stoichiometric byproduct. Despite this kind of reactions have been known for more than thirty years (Scheme 1d,e) [25-27], they did not found significant application in preparative organic chemistry laboratories and industrial production mainly due to the need for pressurized carbon monoxide and high pressure equipment. Aiming to address the issue, we looked for a procedure for the synthesis of carbazoles with broad functional group tolerance, high efficiency and that avoids the need for high-pressure equipment.

2. Experimental

2.1. General methods and materials

Unless otherwise stated, all reactions and manipulations were performed under a dinitrogen atmosphere using standard Schlenk apparatus. All glassware and magnetic stirring bars were kept in an oven at 120 °C for at least two hours and let to cool under vacuum before use. Solvents were dried and distilled by standard procedures and stored under dinitrogen atmosphere. Et_3N and DBU were distilled from CaH_2. Inorganic bases were dried by heating at 180 ºC for 8 h under vacuum, then left to cool down under vacuum. They were weighed in the air but stored under dinitrogen atmosphere to avoid water uptake. Phenyl formate was prepared following a procedure reported in the literature [28]. 1,10-Phenanthroline (Phen) was purchased as hydrate (Sigma-Aldrich). Before use, it was dissolved in CH_2Cl_2, dried over Na_2SO_4, followed by filtration under dinitrogen atmosphere and evaporation of the solvent under vacuum. Phen was weighed in the air but stored under dinitrogen atmosphere to avoid water uptake. $Pd(CH_3CN)_2Cl_2$ [29] and $Pd(OAc)_2$ [30], employed in this work as catalyst precursors, were synthesized from $PdCl_2$ according to procedures reported in the literature. Unless otherwise stated commercially available reagents were purchased from Sigma-Aldrich (Merck), Tokyo Chemical Industries or Fluorochem and used as received. ^1H NMR and ^{13}C NMR spectra were recorded at frequencies of 300 or 400 MHz for the proton and 75 or 100 MHz for the carbon on Bruker Avance 300/400 spectrometers. Chemical shifts are reported in ppm relative to TMS; the data are reported as follows: proton multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, ddd = doublet of doublet of doublet, m = multiplet and br = broad), coupling constants and integration. Elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer. GC quantitative analyses were performed on a DANI 86.10 gas chromatograph equipped with a FID detector using a SUPELCO Analytical SLB™-5ms column (Fused Silica Capillary Column 30 m × 0.32 mm × 0.5 μm film thickness). A standard analysis involves the preparation of a sample solution in CH_2Cl_2 of conc. 0.1 mg/mL calculated with respect to the amount of biphenyl used as an internal standard. A calibration curve was made using biphenyl as the internal standard. The compounds used as

standards were obtained as follow: aminobiphenyl was prepared as previously reported [31], commercial carbazole was recrystallized from ethanol, and commercial *o*-nitrobiphenyl was purchased from Fluorochem and used without further purification. The purity of all the standards used for calibration was checked by ^{1}H NMR and elemental analyses. Synthetic procedures for the synthesis of *o*-nitrobiphenyls and full characterization of isolated carbazoles are described in the Supplementary Materials.

2.2. $Na_2[PdCl_4]$ preparation

The synthesis was adapted from a procedure reported in the literature for the preparation of $Li_2[PdCl_4]$ [32]. $PdCl_2$ (0.50 g, 2.8 mmol) was suspended in distilled water (3 mL) and NaCl (0.33 g, 5.6 mmol) was added. The reaction was heated at 70 °C for 1h until complete dissolution of $PdCl_2$. The obtained brown-red solution was allowed to cool to room temperature and filtered on filter paper by means of a cannula. Water was then evaporated under vacuum affording a brown solid that was smashed into powder and kept under vacuum at 80 °C for 8 h.

2.3. General procedure for catalytic reactions

The catalyst precursors were handled, weighed and stored in the air except for $Pd(OAc)_2$ that was stored under dinitrogen. In order to avoid weighing very small amounts of the catalysts, stock solutions (under dinitrogen) of palladium catalysts were prepared in the appropriate solvent. For catalytic runs that required an amount of Phen less than 10 mg, a stock solution was prepared to avoid large weighing errors. In a typical reaction, the substrate was weighed in the air and placed in a 23 mL heavy-walled glass pressure tube with screw thread (Duran®) containing a magnetic stirring bar. (For an in-depth discussion of the different kinds of pressure tubes that can be employed, and the corresponding advantages and disadvantages see ref. [33]). The tube was placed in a Schlenk tube with a wide mouth. The tube was evacuated and filled with dinitrogen three times to remove air. The catalyst and ligand solutions and the amount of solvent required to reach a total volume of 10 mL were added and the reaction mixture was stirred for 10 min to allow Phen to coordinate to palladium. Finally, HCOOPh and the base were added in this order. The pressure tube was plugged with a Schott PTB screw cap completed with a PTFE-protected seal and immersed in an oil bath preheated at the appropriate temperature. At the end of the reaction, the pressure tube was lifted from the oil and let to cool to room temperature. Then, the screw cap was carefully removed, the excess of CO was vented, and the content was analyzed by GC or subjected to column chromatography. (Caution: evolution of dissolved CO from the solution may continue for several minutes; keep the tube under a hood).

*2.4. Procedure for large scale synthesis of carbazole, **2a***

In a 250 mL Fisher-Porter bottle **1a** (1.61 g, 8.08 mmol), Phen (36 mg, 0.20 mmol, 2.5 mol%), $Na_2[PdCl_4]$ (11.9 mg, 4.04×10^{-2} mmol, 0.5 mol%) and DMF (50 mL) were added in the air and the reaction was stirred for 10 min at RT. Phenyl formate (3.90 mL, 35.6 mmol) and Na_3PO_4 (179 mg, 1.09 mmol) were added. The bottle was closed and transferred to a preheated oil bath. The reaction mixture was heated at 170 ºC with continuous stirring for 16 hours. Then the reactor was lifted from the oil bath and allowed to cool to room temperature. The bottle was carefully opened under a hood and the mixture stirred until evolution of CO ceased. The reaction was filtered to remove Pd-black, then poured into 1M aq. HCl (100 mL) and stirred for ca. 10 min during which a precipitate formed. The reaction mixture was filtered, and the precipitate was washed with a saturated aq. $NaHCO_3$ solution and then water to remove phenol. The solid was then dissolved in CH_2Cl_2 (30 mL) and the solution dried over Na_2SO_4. After filtration, evaporation of the solvent under reduced pressure afforded the pure carbazole **2a** (1.15 g, 85%) as a colorless solid.

*2.5. Procedure for large scale synthesis of Clausine V, **2y***

In a 250 mL Fisher-Porter bottle, 4,4'-dimethoxy-2-nitrobiphenyl (**1y,** 2.15 g, 8.00 mmol), Phen (36 mg, 0.20 mmol, 2.5 mol%), $Na_2[PdCl_4]$ (11.9 mg, 4.04×10^{-2} mmol, 0.5 mol%) and DMF (50 mL) were added in the air and the reaction was stirred for 10 min at RT. Phenyl formate (3.90 mL, 35.6 mmol) and Na_3PO_4 (179 mg, 1.09 mmol) were then added. The bottle was closed and transferred to a preheated oil bath. The reaction mixture was heated at 170 ºC with continuous stirring for 16 hours. Then the reactor was lifted from the oil bath and allowed to cool to room temperature. The bottle was carefully opened under a hood and the mixture stirred until evolution of CO ceased. The reaction was filtered to remove Pd-black, then poured into 1M aq. HCl (100 mL) and stirred for ca. 10 min during which a precipitate formed. The reaction mixture was filtered, and the precipitate was washed with an aq. $NaHCO_3$ solution and then water to remove phenol. The solid was then recrystallized from THF affording **2y** (1.42 g, 78%) as a crystalline colorless solid.

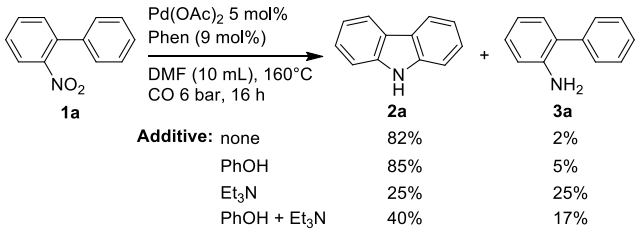
3. Results and discussions

To develop a useful synthetic method to carbazole that fulfills the requirements described above, we focused on the use of CO surrogates, which are stable compounds able to release CO in solution under specific conditions and allow to avoid the use of pressurized gas [34-41]. In this context the group of Driver applied two protocols, initially developed for the synthesis of indoles, to the cyclization of *o*-nitrobiphenyls to carbazoles using respectively $Mo(CO)_6$ [42] and CO_2 [43] as

CO surrogates. Main drawback of the two methods is the need for a two- and three-chambers reactors respectively. Moreover, only one example of carbazole preparation was reported in each paper. In parallel we also reported a novel Pd-catalyzed synthetic method in which formate esters are used as CO surrogates that allowed for the preparation of indoles [33, 44, 45] and oxazines [46] in high yields using cheap, commercially available thick walled glass tubes as reactors. The catalyst employed for the synthesis of indoles was a complex obtained *in-situ* from 1 mol% $Pd(CH_3CN)_2Cl_2$ (**Pd-1**) and 2.5 mol% 1,10-phenanthroline (Phen) in acetonitrile and the carbon monoxide source was phenyl formate, whose decomposition to CO and phenol was catalyzed by triethylamine.

When the latter catalytic system was employed for the synthesis of carbazole from commercially available *o*-nitrobiphenyl, a poor yield (< 5%) was obtained. The result was not completely unexpected since the cyclization of 2-nitrobiphenyls to carbazole using pressurized CO as the reductant is indeed known to be more challenging than that of *o*-nitrostyrenes to indoles, requiring harsher conditions [27]. Even by using relatively high catalyst loading (5 mol%) and temperature (180 °C) the yield of carbazole was still low after 5h (Table S1, Supplementary Material). Gas-chromatographic analysis of the mixture evidenced an almost complete conversion of the substrate but a low carbazole selectivity. 2-Aminobiphenyl (**3a**), obtained by exhaustive reduction of the nitro group, was the main detectable side-product (30% selectivity) and the uncomplete mass balance is explained by formation of 1,3-di([1,1'-biphenyl]-2-yl)urea produced by carbonylation of the formed amine [47]. DMF is often a good solvent for this kind of reactions [20, 27, 48] and led to a doubled carbazole selectivity (Table S1), but the results were still poorer than those previously reported by Smitrovich and Davies using pressurized carbon monoxide [27]. In order to shed some light on the cause of the low selectivity, we performed a series of experiments using pressurized carbon monoxide and in the absence of phenyl formate (Scheme 2). The tests allowed to exclude that the phenol coproduced during phenyl formate decomposition, when this is used as CO surrogate, could be the cause for aniline formation and low carbazole selectivity.

Further control experiments performed using HCOOPh as the CO source, also allowed to exclude adventitious moisture (Table S3 entries 6-8) as the cause of this effect. On the other hand, it was found that it is the presence of triethylamine to cause the low selectivity in carbazole and the formation of 2-aminobiphenyl (**3a**).



Scheme 2. Effect of additives on the reductive cyclization of 2-nitrobiphenyl using pressurized CO. Experimental conditions: **1a** (108 mg, 0.54 mmol), additive: PhOH (2.4 mmol), Et_3N (0.29 mmol). Conversion was >98% in all cases. Percentages refer to selectivities and were determined by gas chromatography using biphenyl as the internal standard. See Table S2 for complete data.

Tertiary amines having hydrogens in the α-position are able to transfer hydrogen to Pd(0) and Pd(II) complexes and to heterogeneous palladium catalysts [49], forming Pd-H species responsible for the nitro group hydrogenation. This side effect of triethylamine was not found during the synthesis of indoles from *o*-nitrostyrenes because the cyclization step, that follows an initial reduction of nitro group to nitroso, is faster than for *o*-nitrobiphenyls [20].

Starting from these preliminary results, we optimized the reaction conditions. Given the detrimental effect of triethylamine, we aimed at its replacement. A number of bases both organic and inorganic are effective in promoting HCOOPh decomposition to CO and phenol [50]. However other tertiary amines such as DBU produced the same effect of triethylamine (Figure 1, see Table S3 for complete data).

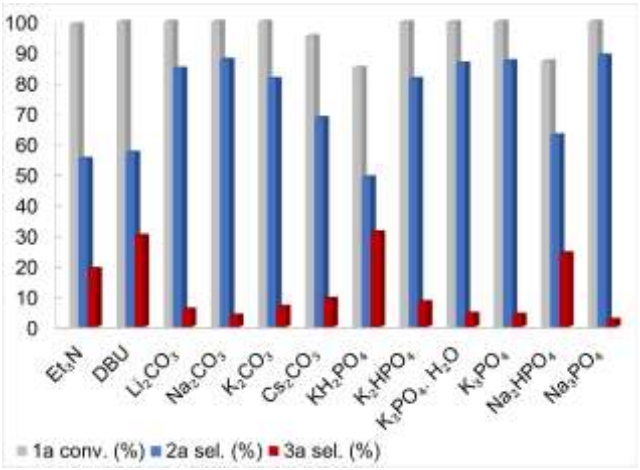


Figure 1. Pd-catalyzed reductive cyclization of 2-nitrobiphenyl to carbazole: effect of different bases. The reactions were performed in a pressure tube: **1a** (0.54 mmol), **Pd-1** 5 mol%, Phen 9 mol%, HCOOPh (2.4 mmol), base (0.15 mmol) in DMF (10 mL) at 160 °C for 5h. Reagent conversion and product selectivities were determined by gas chromatography.

Among the inorganic bases tested, all carbonates and phosphates gave better results than triethylamine, with the only exception of the little basic KH_2PO_4. Sodium salts afforded slightly better carbazole selectivities than potassium ones. Na_3PO_4 afforded the best results and was effective also when its loading was decreased from 28 to 7 mol% (Table S3 entries 13-14). A screening of different polar aprotic solvent (Table S4) confirmed DMF as the best reaction medium.

A series of experiments performed at different temperatures showed that the reaction can be run at temperature lower than 160 °C but at a slight expense of activity and selectivity: best results were obtained at 170 °C (Table S5).

The more strongly donating 4,7-dimethoxy-1,10-phenanthroline was also tested as ligand at 120 and 140 °C, in the hope that its use may allow for a higher reactivity and possibly a better selectivity then phenanthroline. In previous studies in our group [51, 52], this was the ligand that allowed to obtain best results when difficult to reduce nitro compounds were used. However, despite a slightly higher conversion could be reached with respect to that observed for phenanthroline at 120 °C, selectivity in carbazole was lower at both temperatures (Table S5) and the use of the substituted ligand was not pursued any further.

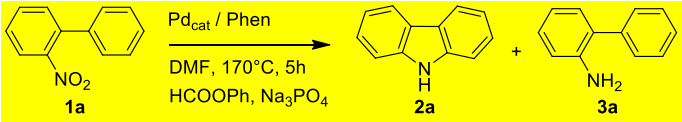
In the aim of optimizing the system for a wide applicability both on a small and a large scale, we tried to reduce the reaction time and the catalyst loading. At 5 mol% of palladium loading, full conversion was still obtained when the reaction time was halved (Table 1, entries 1-2). Unfortunately, the use of shorter reaction times and lower palladium loadings evidenced a stability problem of the catalytic system (Table 1, entries 3-5). The nitroarene was initially converted quickly, reaching 87% conversion in 1h, but then the reaction became sluggish (entries 4-6). We found that addition of chlorides stabilizes the catalytic system (Table S6). This led us to test $Na_2[PdCl_4]$ (**Pd-2**) as the pre-catalyst, which showed higher stability and allowed us to decrease the catalyst loading to 0.1 mol% (Table 1, entry 7). Interestingly, when 1 mol% of **Pd-2** was employed as the catalyst the system was stable even when the pressure tube was closed in the air, instead of N_2, and employing commercial undried DMF (Table 1, entries 9-10). Nevertheless, when 0.1 mol% of catalyst was used, air was less tolerated (entry 12).

We had also tested the system in the absence of any ligand. Only a 4 % yield in carbazole was obtained, mostly due to a low conversion (9 %). Selectivity was also low (48 %) anyway (entry 13).

A comparison was made with a reaction run in an autoclave under 6 bar CO, the best pressure according to the previously mentioned work of Smitrovich and Davies [27] with a related catalytic system. The conversion was markedly lower, although the selectivity in carbazole remained high (entry 14). Even if we have not optimized the reaction conditions for the reaction under CO pressure, this experiment confirms that, analogously to what observed for several related reactions

[44-46] the use of a CO surrogate should not be considered only a second choice when use of pressurized CO is not possible, but may represent the best option in any case.

Table 1. Selected data for the Pd-catalyzed reductive cyclization of 2-nitrobiphenyl to carbazole.[a]



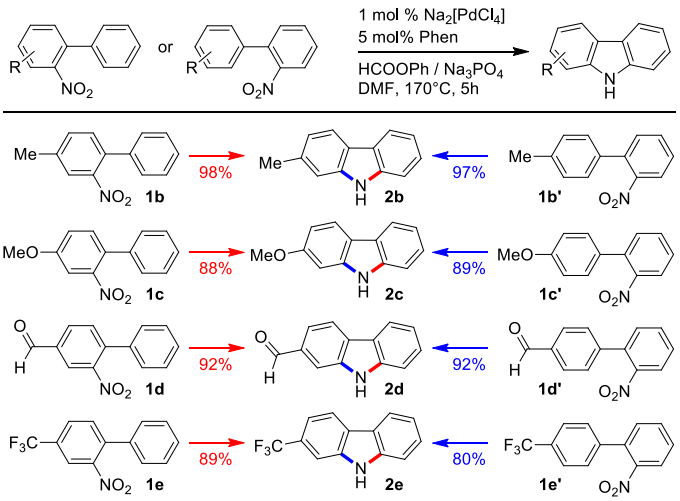
entry	cat. (mol%)	time (h)	conv. (%)	**2a** select. (%)	**2a** yield (%)
1[b]	Pd-1 (5)	2	100	92	92
2[b]	**Pd-1** (5)	1	100	92	92
3	**Pd-1** (2)	1	93	89	83
4	**Pd-1** (1)	1	87	86	75
5	**Pd-1** (1)	2	94	91	86
6	**Pd-1** (1)	5	98	91	89
7	**Pd-2** (1)	2	100	91	91
8	**Pd-2** (1)	5	100	95	95 (93)[c]
9[d]	**Pd-2** (1)	5	100	97	97
10[d, e]	**Pd-2** (1)	5	100	94	94
11	**Pd-2** (0.1)	16	95	97	92
12[d, e]	**Pd-2** (0.1)	16	23	78	18
13[f]	**Pd-2** (1)	5	9	48	4
14[g]	**Pd-2** (1)	5	23	91	21

[a]Experimental conditions: **1a** (0.54 mmol), Phen 5 mol%, HCOOPh (2.4 mmol), Na_3PO_4 (7.3×10^{-2} mmol) in DMF (10 mL) at 170 °C. Reactions were performed in a glass pressure tube. Conversion and yield were determined by gas chromatography. [b]Phen 9 mol%. [c]Isolated yield. [d]Reaction assembled in the air. [e]Undried and undistilled DMF was used. [f] Reaction run in the absence of any added phenanthroline. [g] Reaction run in an autoclave under 6 bar CO and in the absence of any phenyl formate.

Under the optimized conditions, we explored the scope of the reductive cyclization of substituted *o*-nitrobiphenyls. The substrates were mainly prepared through Suzuki-coupling (see SM) from generally inexpensive reagents. To ensure full conversion even of substrates with low reactivity, 1 mol% of **Pd-2** was used with a reaction time of 5 h. At first, a series of substrates bearing electron-donating (EDG) or electron-withdrawing (EWG) groups either in the 4 or 4' positions (Scheme 3) were tested. The high yields obtained when the substituents are on the ring bearing the nitro group are almost the same of those obtained when the substituent is on the other ring. The only exception is substrate **1e'** that yielded **2e** in slightly lower yield with respect to **1e** due to the presence of the strongly electronwithdrawing trifluoromethyl. The result can be explained by the reaction mechanism proposed by us for this kind of cyclizations [20]. In fact, the cyclization

step occurs after the initial reduction of the nitro group to nitroso and involves an electrophilic attack of the latter on the opposite aromatic ring, which for substrate **1e'** is an electron-poor ring.

Scheme 3. Synthesis of carbazoles: effect of substitution on the two rings of 2-nitrobiphenyls.[a]

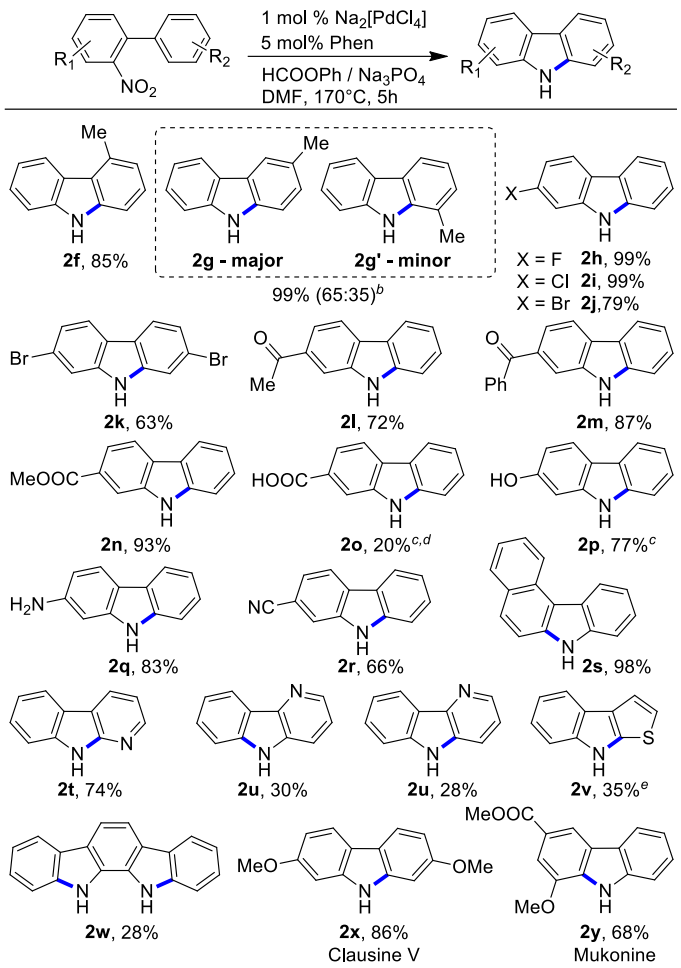


[a]Experimental conditions: **1** (0.54 mmol), HCOOPh (2.4 mmol), Na_3PO_4 (7.3×10^{-2} mmol) in DMF (10 mL). Reactions were performed in a glass pressure tube. Percentages refer to isolated yields.

Alkyl groups on the ring not bearing the nitro group are well tolerated when in *ortho* (**1f**), *para* (**1b'**) and *meta* (**1g**) position (Chart 1). In the latter case two isomers are obtained, with that deriving from the closure *para* to the methyl group (**2g**) prevailing, likely for steric reasons. Quantitative yields were obtained when fluoride and chloride (**2h**, **2i**) substituents are present. The presence of bromide is less tolerated due to a possible oxidative addition of the C-Br bond to Pd center, which leads to side reactions. Still, even in the case of **2j** the yield was very good. Noteworthy, the dibrominated carbazole **2k**, an important intermediate in the preparation of compounds and materials with light-emitting and photovoltaic applications [53-55], was also obtained in good yield. -OMe (**2c**), -CHO(**2d**), -COOMe (**2n**) and -OH (**2p**) groups which are present in many biological active carbazole scaffolds [3] are well tolerated. It should be mentioned that using pressurized carbon monoxide cyclization of **1c** to **2c** has been reported to occur only in 22% yield [27] while the direct synthesis of **2p** was previously reported only using PPh_3 as the reductant, albeit in low yield, 33% [10].

Remarkably, two natural occurring carbazoles, used as drugs due to their biological activity, Clausine V (**2x**) and Mukonine (**2y**) were synthesized respectively in 86% and 68% yields. On the other hand, the presence of a free carboxylic acid (**2o**) lowered the yield substantially, likely because the acid is deprotonated by the base under the reaction conditions and the anionic substrate is less easily reduced. However, it should be mentioned that **2o** can be conveniently obtained by

Chart 1. Substrate scope.[a]

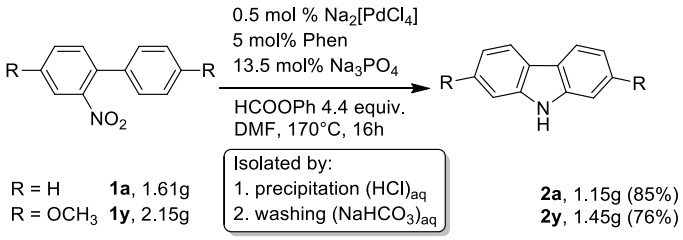


[a]Experimental conditions: **1** (0.54 mmol), HCOOPh (2.4 mmol), Na_3PO_4 (7.3×10^{-2} mmol) in DMF (10 mL). Reactions were performed in glass pressure tubes. Percentages refer to isolated yields. [b]Isolated yield refers to the sum of the two isomers. The isomeric ratio, in parentheses, was calculated from GC analysis. [c]The reaction mixture was acidified before separation. [d]Also obtained by hydrolysis of **2n** in 95% yield. [e]$Na_2[PdCl_4]$ 2 mol%, 4,7-dimethoxyphenanthroline 5 mol% for 16 h.

hydrolysis of the corresponding methyl ester (**2n**, 95% yield from the ester), whose synthesis proceeds in high yields. To our surprise, a substrate bearing unprotected -NH_2 group, which is generally not compatible with the Pd-catalyzed reductive cyclization of nitroarenes reactions, was cyclized to the corresponding carbazole (**2q**) in a very good yield. Among a series of fused polyheterocycles (**2t**-**2v**), α-carboline (**2t**) was the only one isolated in good yield. Only trace amounts of 8*H*-thieno[2,3-*b*]indole (**2v**) were obtained under standard conditions, but the yield reached 35% when prolonging the reaction time and using 4,7-dimethoxy-1,10-phenanthroline as ligand [51], indicating that a further optimization of the conditions is needed for the cyclization of hetero-nitroaryls. Double cyclization of 2,3-dinitro-1,1'-terphenyl afforded the corresponding indolocarbazole (**2w**) in only 28% yield. Though the result is not outstanding, the difficulty of

double cyclization in *o*-dinitro compounds [56] and the importance of indolocarbazoles in medicinal and materials chemistry [57] makes the result promising for future developments. A partial cause of the low reactivity of **1w** is the steric hindrance given by the presence of two adjacent nitro groups. The same detrimental effect of a substituent *ortho* to -NO_2 was evidenced in an attempt to cyclize methyl 5-methoxy-6-nitro-[1,1'-biphenyl]-3-carboxylate (**1y'**) which afforded Mukonine (**2y**) in only 6% yield even after 16h.

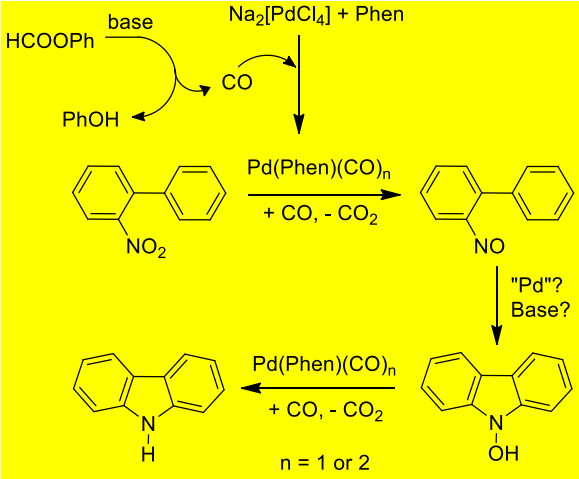
Finally, we performed a gram scale synthesis of carbazole (**2a**) and Clausine V (**2x**) using 15-fold substrate amount, 0.5 mol% Pd catalysts and decreasing the solvent amount to one third of the calculated volume in order to facilitate the work-up. The reaction vessel was closed in the air and commercial DMF was used. Noteworthy, both carbazoles were isolated by precipitation with water. Simple washing of the solid, in case followed by recrystallization, afforded the pure products in 85% (**2a**) and 78% (**2x**) yield. Note that this purification strategy was not optimized. Thus, higher isolated yields may likely be obtained.



Scheme 4. Gram-scale application of the synthetic method.

The possibility of scaling up the procedure without the need for strictly oxygen-free conditions and avoiding expensive and time-consuming chromatographic purification is clearly a strength point of the described synthetic method, which makes it suitable for medium to large-scale preparations.

As far as the reaction mechanism is concerned (Scheme 5), phenyl formate decomposition by bases [28, 44] produces the CO necessary for the initial reduction of the palladium(II) precursor to the active palladium(0) phenanthroline carbonyl complex and for the further reduction of the nitro group. Reaction of the reduced palladium complex with nitrobiphenyl affords the corresponding nitrosoarene, as generally accepted for different reduction reactions of nitroarenes by CO.



Scheme 5. Proposed reaction mechanism.

Theoretical calculations showed that the cyclization of *o*-nitrosobiphenyl to yield *N*-hydroxycarbazole is energetically accessible even in the absence of any metal or base, although a possible acceleration of this reaction by metal complexes or bases was not investigated [58]. The intermediate formation of *N*-hydroxycarbazoles has not been experimentally observed during previous studies on the reductive cyclization of *o*-nitrobiphenyls but *N*-hydroxy derivatives have been observed in related cyclization reactions [20, 59] and their reduction by metal carbonyl complexes to the corresponding N-H compounds experimentally proved [60]. The latter reduction also constitutes the final step of the present catalytic cycle and is surely metal-catalyzed.

A mechanistic study is in progress in our laboratories on the reductive cyclization of *o*-nitrobiphenyl to carbazole by CO and the results so far collected are in agreement with the general pathway shown in Scheme 5. An active role of the base in catalyzing not only the formate decomposition, but also the cyclization of *o*-nitrosobiphenyl emerged from the preliminary data.

4. Conclusions

In summary, we developed an efficient new procedure for the synthesis of carbazoles starting from *o*-nitrobiphenyls. The catalytic method makes use of $Na_2[PdCl_4]$/Phen as catalyst together with phenyl formate as an *in-situ* CO source, which acts as the reductant for the nitro group. Critical aspects for the stability of the catalytic system have been identified and the system optimized in order to perform the reaction using a low catalyst loading (Substrate/Pd = 1000:1, corresponding to a catalyst amount lower than any previously employed amount for this kind of cyclization using either CO or CO-surrogates). The easy synthesis of the starting materials by cross-coupling reactions and the high functional group tolerance allow to synthesize a variety of carbazoles with potential pharmaceutical and materials applications in high yields. The overall procedure is easily

scalable, and the products can be isolated without chromatographic purification. In addition, the reaction tolerates moisture and air. The features of the herein presented methodology make this synthetic method a versatile and cheap tool for the synthesis of carbazole that has potential for replacing Cadogan-type reactions, still widely used for the synthesis of heterocycles even on an industrial scale.

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Graphical Abstract