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Synthesis of Indoles by Intermolecular Cyclization of Unfunctionalized Nitroarenes and Alkynes, Catalyzed by Palladium−Phenanthroline Complexes

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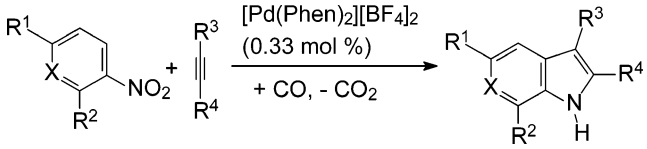

Palladium−phenanthroline complexes efficiently catalyze the reaction of nitroarenes with arylalkynes and CO to give 3-arylindoles by an *ortho*-C−H functionalization of the nitroarene ring. Both electron-withdrawing and electron-donating substituents are tolerated on the nitroarene, except for bromide and activated chloride. Nitroarenes bearing electron-withdrawing substituents react faster, but the selectivity of the reaction depends on both polar and radical stabilization effects. Among those tested, only arylalkynes afforded indoles under the investigated conditions. The reaction mechanism was partly investigated. The kinetics is first order in nitroarene concentration and the rate-determing step of the cycle is the initial nitroarene reduction. No primary isotope effect is observed on either rate or selectivity, implying that the cyclization step is fast.

Introduction

The indole skeleton is part of many pharmaceutically active molecules, and its synthesis continues to attract much interest,[1] but the overwhelming majority of the reported synthetic strategies require the availability of a nitrogen-functionalized arene (e.g., an arylamine or a nitroarene[2−5]) also having a suitable functional group in the ortho position with respect to the nitrogen substituent. Penoni and Nicholas have recently reported that $[RuCp^*(CO)_2]_2$ catalyzes the reaction of nitroarenes with alkynes to give indoles.[6] The presence of a substituent in the ortho position of the nitroarene is not required. Selectivities are only moderate, but the procedure saves several synthetic steps. The reaction is new and interesting, but, in our view, its application is severely limited by the low activity of the catalyst. Despite the fact that the substrate/Ru ratio is only 10, the reaction takes 48 h at 170 °C to be complete. Some experimental evidence was provided that the reaction proceeds via the nitrosoarene, which reacts with the alkyne in an off-metal reaction to afford the *N*-hydroxyindole.[7,8] Palladium−phenanthroline complexes are at present the most active catalysts for reductive carbonylation of nitroarenes,[9−11] and we have recently shown that $[Pd(phen)_2][BF_4]_2$ is an excellent catalyst for the synthesis of oxazines and *N*-arylpyrroles from nitroarenes and conjugated dienes.[12] This reaction also apparently proceeds by

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(8) Just before submission of this paper, the same authors have reported the extension of the reaction based on the use of the nitrosoarenes to the synthesis of *N*-methoxyindoles: Penoni, A.; Palmisano, G.; Broggini, G.; Kadowaki, A.; Nicholas, K. M. *J. Org. Chem.* **2006**, *71*, 823−825.
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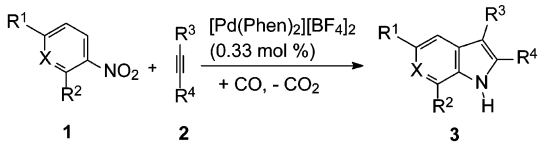
SCHEME 1



Nitroarenes				Alkynes		
R^1	R^2	X		R^3	R^4	
H	H	CH	**1a**	C_6H_5	H	**2a**
Cl	H	CH	**1b**	C_6H_5	CH_3	**2b**
CH_3	H	CH	**1c**	C_5H_{11}	H	**2c**
$C(O)OCH_3$	H	CH	**1d**	$C(O)OCH_3$	$C(O)OCH_3$	**2d**
OCH_3	H	CH	**1e**	C_6H_5	C_6H_5	**2e**
H	Cl	N	**1f**	$C(CH_3)CH_2$	H	**2f**
$OC(O)CH_3$	H	CH	**1g**	CH_2CH_3	CH_2CH_3	**2g**
NO_2	H	CH	**1h**	C_6H_4-4-NH_2	H	**2h**
CN	H	CH	**1i**	C_6H_4-4-OCH_3	H	**2i**
H	CH_3	CH	**1j**	C_6H_4-4-Cl	H	**2j**
				C_6H_4-4-C_6H_5	H	**2k**
				C_6H_4-4-CF_3	H	**2l**
				C_6H_4-4-CH_3	H	**2m**
				$Si(CH_3)_3$	$Si(CH_3)_3$	**2n**

a metal-catalyzed reduction of the nitroarene to nitrosoarene, followed by an off-metal reaction with the diene. Thus, we considered that the same catalyst would also perform well in the synthesis of indoles. This expectation was confirmed to be true, although the experimental conditions originally optimized for the oxazines were not suitable for the synthesis of indoles.

Results and Discussion

Synthetic Results. A list of the nitroarenes and alkynes investigated in this study is shown in Scheme 1.

Nitrobenzene (**1a**) and phenylacetylene (**2a**) were chosen for the optimization of the experimental conditions. 3-Phenylindole (**3aa**; in the numbering of indoles, the first letter refers to the nitroarene and the second to the alkyne employed) was the only detected product containing both the nitrobenzene- and the phenylacetylene-derived moieties. Not a trace of the isomeric 2-phenylindole was detected. This is noteworthy, because most reported syntheses of arylindoles selectively afford the 2-substituted product, and few methods exist for the 3-substituted isomer.[13,14] The major nitrobenzene-derived byproduct was azoxybenzene, but minor amounts of azobenzene and aniline were also formed. Diphenylurea was detected, but could not be quantified by gas chromatographic analysis, because it decomposed during the analysis. Small amounts of a phenylacetylene dimer and of the coupling compound PhC≡C−C≡CPh were the only alkyne-derived byproducts.

The main results of the optimization study are the following. (i) The reaction is slow at temperatures below 130 °C, and its rate increases with an increase in the temperature up to 190 °C. (ii) The selectivity is almost constant in the range 130−170 °C but decreases at higher temperatures. Thus, we chose 170 °C as the standard temperature. (iii) The selectivity in indole is almost independent of the CO pressure between 20 and 60 bar, but decreases outside this range. However, the amount of phenylacetylene-coupling products strongly decreases with the CO pressure, and 60 bar was chosen as the operating pressure for this reason. Under these conditions (170 °C, 60 bar), the alkyne dimers are barely detectable by GC-MS. (iv) Medium polarity, aprotic solvents, THF, and 1,2-dimethoxyethane (DME) are the best solvents. More polar solvents such as DMF give a faster but less-selective reaction, while lower polarity solvents (diethyl ether, dioxane) give a slower reaction without any increase in selectivity with respect to THF and DME. (v) The addition of bases or acids strongly inhibits the reaction. (vi) The amount of phenanthroline and phenylacetylene were also optimized, and the values employed for the reactions in Table 1 are the best ones. Under these conditions, a complete conversion of nitrobenzene was achieved in 3 h with a 0.33 mol % catalyst and affording 3-phenylindole in a 53% yield. A comparison with the published data shows that $[Pd(phen)_2][BF_4]_2$ is almost 500 times more active than $[RuCp^*(CO)_2]_2$ (based on the number of metal atoms) at the same temperature,[6] although the selectivity in indole is only marginally improved (39% with ruthenium). The palladium catalyst is also cheaper and easier to prepare, making the present synthetic strategy now competitive.

Some experiments were also conducted employing nitrobenzene as substrate, but in the presence of 4-toluidine. In no case were indoles, azo-, or azoxy-arenes containing the methylated arene detected, showing that anilines are not intermediates in the formation of any of these products.

The results of a series of experiments that were run with 1-phenylpropyne (**2b**), but different nitroarenes, are reported in Table 1. This alkyne was chosen because the presence of a methyl group allowed the quantification of the indole produced by ^{1}H NMR of the crude reaction mixture without workup, although all indoles were later isolated and fully characterized. The experimental conditions optimized with **1a** and **2a** were employed, except for the reaction time that was increased to 10 h as a result of the lower reaction rate observed with this disubstituted alkyne. In all cases, only the regioisomer with the aryl group in the 3-position was obtained. In the table, the Hammett σ values for the substituents on the nitroarene[15] are also reported, together with a parameter, $\sigma_{JJ\bullet}$, which describes radical stabilization effects.[16]

TABLE 1. Synthesis of Indoles from 1-Phenylpropyne and Different Nitroarenes[a]

$ArNO_2$	R^1	$ArNO_2$ conv.[b,c] (%)	indole sel.[d] (%)	σ_{Hamm}	$\sigma_{JJ\bullet}$
1a	H	68.4	29.7 (**3ab**)	0	0
1b	Cl	25.8	21.5 (**3bb**)	0.23	0.22
1c	CH_3	74.1	36.7 (**3cb**)	−0.17	0.15
1d	$C(O)OCH_3$	90.4	28.7 (**3db**)	0.45	0.33
1e	OCH_3	52.3	44.7 (**3eb**)	−0.27	0.23
1f		1.6			
1g	$OC(O)CH_3$	100	31.4 (**3gb**)	0.31	0.35
1h	NO_2	100	24.3 (**3hb**)	0.78	0.36
1i	CN	100	14.6 (**3ib**)	0.66	0.42
1j		44.7	8.2 (**3jb**)		

[a] Experimental conditions: $[Pd(phen)_2][BF_4]_2 = 4.7 \times 10^{-3}$ mmol, mol ratios Pd/phen/nitroarene/PhC≡CCH_3 = 1:20:300:1800, T = 170 °C, P_{CO} = 60 bar, in DME (10 mL), for 10 h. [b] Calculated with respect to the starting nitroarene. [c] Measured by GC with naphthalene as the internal standard. [d] With respect to the reacted nitroarene, measured by ^{1}H NMR, with 2,4-dinitrotoluene as the internal standard.

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TABLE 2. Synthesis of Indoles from 4-Nitrotoluene and Different Alkynes[a]

alkyne	group in the 4-position on ArC≡CH	**1c** conv[b,c] (%)	indole sel.[d] (%)	σ_{Hamm}	$\sigma_{JJ\bullet}$
2a	H	100	29.9 (**3ca**)	0	0
2e		100	38.1 (**3ce**)		
2h	NH_2	100	23.2 (**3ch**)	−0.66	1.00[e]
2i	OCH_3	100	33.7 (**3ci**)	−0.27	0.23
2j	Cl	100	16.1 (**3cj**)	0.23	0.22
2k	C_6H_5	100	11.9 (**3ck**)	−0.01	0.47
2l	CF_3	100	9.3 (**3cl**)	0.54	−0.01

[a] Experimental conditions: $[Pd(phen)_2][BF_4]_2 = 4.7 \times 10^{-4}$ mmol, in DME (1 mL); other conditions as in Table 1. [b−d] See corresponding footnotes in Table 1. [e] Value for $-NMe_2$.

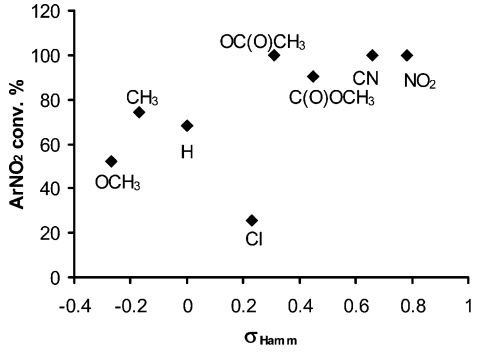

FIGURE 1. Nitroarene conversion against the Hammett σ constant for the reactions in Table 1.

Another series of experiments were run keeping the nitroarene (4-nitrotoluene) constant and changing the alkyne. Positive results are reported in Table 2. The reactions were performed under the same experimental conditions of Table 1, but on a smaller scale.

From the results reported in Table 1, it is immediately evident that both electron-withdrawing and electron-donating substituents in the para position of the nitroarene are tolerated (Figure 1), but a methyl group in the ortho position slows down the reaction and lowers the selectivity.[17] In the case of 2-chloro-3-nitropyridine (**1f**) only, the reaction failed completely, and the substrate was recovered essentially unaltered.

Because the reactivity of 4-chloronitrobenzene was also lower than expected based on the electron-withdrawing power of chlorine (Figure 1), we suspected that activation of the C−Cl bond in the nitroarene was occurring. We recall that compounds of the kind $Pd(phen)X_2$ (X = halogen) are notoriously inactive in nitroarene reductive carbonylation reactions[2,18] and that activation of the C−Cl bond by palladium is known to be easier when electron-withdrawing groups are present on the aryl ring.[19,20] The C−Cl bond in **1f** is, thus, doubly activated by the contemporary presence of a pyridine ring and a nitro group. To test this assumption, two experiments were undertaken. First, a catalytic reaction employing 4-bromonitrobenzene was attempted. Because the C−Br bond is activated more easily than the C−Cl bond, the deactivation effect should be even more evident. In accord with our hypothesis, no indole was formed at all, and the amount of 4-bromonitrobenzene at the end of the reaction was indistinguishable (by GC) from the initially added one.[21] Second, the reaction of $[Pd(phen)_2][BF_4]_2$ with respect to 4-chloronitrobenzene was tested under the catalytic reaction conditions but in the absence of any alkyne. Because the catalyst amount under usual conditions is too small (less than 1 mg of palladium) to isolate any organometallic product, the catalyst amount was increased 10-fold and the reaction time was also prolonged to 10 h. At the end of the reaction, an insoluble precipitate was present, which was dissolved in DMSO-d_6 and analyzed by ^{1}H NMR. Comparison with the signals of an authentic species showed that about half of the residue is indeed $Pd(phen)Cl_2$, although a second major species and at least a third one present in a much lower amount are present also. These last two species could not be identified but are not the starting complex.[22] Thus, it can be conclusively stated that the lower or null reactivity observed with halonitroarenes is due to the carbon−halogen bond activation by the palladium catalyst.

As far as the alkyne series is concerned, only arylalkynes afforded the indole. Nitroarene conversion was fast (100% conversion) in the presence of alkylalkynes (**2c**, **2g**), but not even a trace of the cyclized product was formed. An alkenylalkyne (**2f**) gave a mixture of products, apparently mostly derived from a "diene-type" reactivity.[12] Dimethylacetylenedicarboxylate (**2d**) completely inhibited the reaction. Because this alkyne is known to dimerize in the presence of palladium complexes with chelating nitrogen ligands,[23] it is likely that a related reactivity is involved here. Bistrimethylsilylacetylene (**2n**) gave a low conversion (30%) and no indole. Several substituents on the aryl ring of the arylalkynes were tolerated, including a free amino group. This is noteworthy, because many synthetic procedures for the synthesis of indoles would not tolerate such a functional group. Surprisingly, the reaction did not proceed with tolylacetylene (**2m**). However, the commercially available compound was found (by GC-MS) to be contaminated by brominated impurities (2-bromo-4-methylstyrene, β-bromo-4-methylstyrene, and bromomethyl-4-tolyl ketone) that would cause catalyst deactivation (see above). After we purified **2m** to the point that the impurities were no longer observable by GC-MS, the catalytic reaction partially proceeded and the formation of the expected indole (**3am**) was observed by GC-MS. However, the reaction was still incomplete. We note that at the alkyne/palladium ratio employed in the catalytic reactions, a 0.05 mol % amount of brominated impurities in the alkyne would be enough to deactivate all of the catalyst.[24]

A methyl group on the other terminal position of phenylacetylene (**2b**) slows down the reaction (compare Table 1), but the second phenyl group in diphenylacetylene (**2e**) accelerates it.

(17) The lower selectivity may be due to the availability of only one ortho position on the nitroarene, but the lower conversion is likely due to a more difficult reduction of the nitroarene, which appears to be the slow step of the reaction (see also later). Due to the low yield of this indole, it could not be isolated in a pure form, and the identification of **3jb** is to be considered only as a proposal.

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(20) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665−1673.

(21) Since only a 0.33 mol % catalyst was employed, a complete conversion to $Pd(phen)Br_2$ would consume only 0.66% of the starting nitroarene, making it impossible to detect its consumption.

(22) Wehman, P.; Kaasjager, V. E.; Delange, W. G. J.; Hartl, F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Fraanje, J.; Goubitz, K. *Organometallics* **1995**, *14*, 3751−3761.

(23) van Belzen, R.; Elsevier, C. J.; Dedieu, A.; Veldman, N.; Spek, A. L. *Organometallics* **2003**, *22*, 722−736.

(24) Purification of **3cm** proved difficult because this indole and the starting **1c** shows very close R_f values in a chromatographic separation. An analytically pure sample of **3cm** could not be obtained, and accordingly, this compound is not mentioned in the tables or in the Experimental Section.

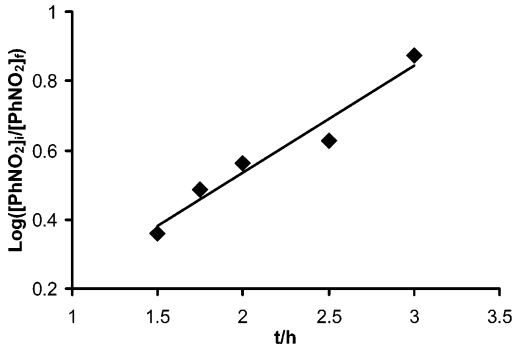

FIGURE 2. Plot of $\log([PhNO_2]_i/[PhNO_2]_f)$ vs reaction time for a series of reactions between **1a** and **2a**. $[Pd(phen)_2][BF_4]_2 = 1.67 \times 10^{-3}$ mmol; mol ratios **1a**/**2a**/phen/Pd = 900:5400:20:1, at 170 °C, $P_{CO} = 60$ bar, and in 1,2-dimethoxyethane (10 mL). The straight line is the best linear fit to the data ($R^2 = 0.96$).

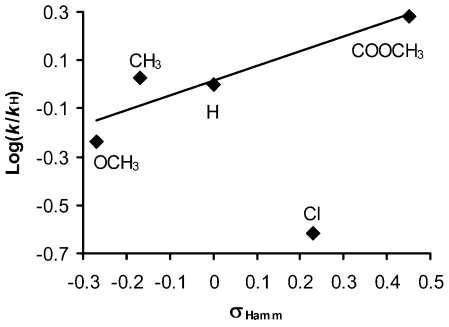

FIGURE 3. Plot of $\log(k/k_H)$ vs Hammett σ, where k is the second-order rate constant for the carbonylation of all nitroarenes for which a total conversion was not observed and k_H is the same constant for nitrobenzene. The straight line ($\rho = +0.61$, $R^2 = 0.85$) is the best linear fit to the data, with the exclusion of the point corresponding to $4\text{-}ClC_6H_4NO_2$.

Reactivity Trends and Mechanistic Aspects. Before analyzing in more detail the results, it is useful to recall some mechanistic information. Reduction of nitroarenes by CO initially produces nitrosoarenes, and the reaction is accelerated by electron-withdrawing substituents.[2] No mechanistic information is available on the reaction between nitrosoarenes and alkynes, but the reaction with alkenes (nitroso-ene reaction)[25] has been investigated even from a theoretical point of view.[26] The nitrosoarene and alkene interact to initially generate a polarized adduct with partial diradical character. This in turn rearranges by abstracting a hydrogen atom on the allylic position of the olefin to give the finally observed allylhydroxylamine. The nitroso-ene reaction is also favored by electron-withdrawing substituents on the nitrosoarene.[25] In the case of the reaction between nitrosoarenes and alkynes, propargylic hydrogens are either not present or their abstraction appears not to be possible, probably for geometric reasons, so that the reaction takes another pathway.

To get more information on the reaction mechanism, the kinetics of the reaction between **1a** and **2a** was investigated. The previously optimized conditions were employed, but the catalyst amount had to be decreased to 0.11 mol % to avoid a complete consumption of the nitroarene. Plotting $\log([PhNO_2]_i/[PhNO_2]_f)$ versus reaction time ($[PhNO_2]_i$ and $[PhNO_2]_f$ are the nitrobenzene concentration, respectively, at the beginning and at the end of the reaction) for a series of reactions between **1a** and **2a**, a straight line is obtained, indicating a first-order dependence of the reaction rate on the nitroarene concentration (Figure 2).

We can now examine the synthetic results in more detail. As previously mentioned, a quick examination of the data in Table 1 immediately shows that nitroarenes having electron-withdrawing substituents generally showed higher reactivity, and for most of them, a complete conversion was observed (Figure 1). Because we have determined that the reaction rate is first order in nitroarene concentration, the kinetic constants (assuming also a first-order rate dependence on palladium concentration, as is always found for this kind of catalytic systems) for all reactions that did not reach complete conversion could be determined, and a plot of $\log(k/k_H)$ versus the Hammett σ constant of the substituents, where k is the second-order rate constant for a generic nitroarene and k_H is the same constant for nitrobenzene, could be drawn (Figure 3). Although the number of useful data points is limited, it is evident that a linear correlation exists, with the remarkable exception of the point due to 4-chloronitrobenzene (**1b**), and a positive slope ($\rho = +0.61$) is observed. The reason for the anomalous behavior of halogen-substituted nitroarenes has been already discussed previously. On the other hand, all the other data, first-order dependence of the rate on nitroarene concentration, positive slope in the Hammett plot, and lower reactivity of 2-nitrotoluene with respect to 4-nitrotoluene,[27,28] indicate that the rate-determining step of the cycle is the initial activation of the nitroarene and are consistent with an electron transfer from the metal to the nitroarene in this step. The latter is a common feature of these reactions and has been observed for all other systems for which this step has been investigated.[2,29,30]

The selectivity in indole is correlated with the ratio between the rate of formation of indole and the rate of formation of possible byproducts. Other factors being constant, this ratio is the function of the substituents on the nitroarene. No evident clear correlation exists between the log(selectivity in indole) and the Hammett σ constant or the σ_{JJ}, alone for the reactions in Table 1. However, a multivariate correlation including both individuates a straight line passing close to all data except for the points for the 4-chloro and the 4-cyano groups (Figure 4). The reason for the deviation of the chlorinated derivative has already been discussed. The reason for which also the cyano substituent gives a lower selectivity than expected is not obvious, but it must be recalled that nitriles can coordinate to palladium. It may be also noticed that the cyano group itself contains a triple bond that may enter in competition with the C≡C one,

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(26) Leach, A. G.; Houk, K. N. *Org. Biomol. Chem.* **2003**, *1*, 1389−1403.

(27) It is well-known that ortho-substituted nitroarenes are more difficult to reduce than the corresponding meta- and para-substituted isomers, because steric hindrance causes a tilting of the nitro group out the arene plane, making charge delocalization in the reduced species more difficult.[28]
(28) Wheeler, O. H. *Can. J. Chem.* **1963**, *41*, 192−194.
(29) The ρ value determined in this study is much lower than that measured by Gladfelter in a study on the reduction of nitroarenes by $Ru(CO)_3(Ph_2P{-}CH_2CH_2PPh_2)$ (+3.45).[30] However, this difference is to be expected because Gladefter's study was conducted at 25 °C, whereas our reactions were performed at 170 °C. Because the nitroarene reduction becomes easier at higher temperatures, both ΔG and $\Delta\Delta G$ values for different nitroarenes will decrease. This will accordingly affect the differences in rate constants and result in a lower slope in the Hammett plot.
(30) Skoog, S. J.; Gladfelter, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 11049−11060.

TABLE 3. Use of Deuterated Nitrobenzene[a]

$PhNO_2$-d_5: $PhNO_2$	$PhNO_2$ conv.[b,c] (%) (H/D mol ratio)[e]	indole sel.[c,d] (%) (H/D mol ratio)[e]	PhN(O)=NPh sel.[c,d] (%) (H/D mol ratio)[e]
0:1	49.5	53.5	20.4
1:0	50.5	50.3	21.2
0.5:0.5	49.9 (0.85)	48.4 (1.08)	18.8 (1:2.3:1.3)[f]

[a] Experimental conditions: $[Pd(Phen)_2][BF_4]_2 = 4.7 \times 10^{-4}$ mmol; mol ratios Pd/phen/$PhNO_2$/PhC≡CH = 1:20:300:1800, T = 170 °C, P_{CO} = 60 bar, in DME (1 mL) for 1 h. [b] Calculated with respect to the starting nitroarene. [c] Measured by GC with naphthalene as the internal standard. [d] With respect to the reacted nitrobenzene. [e] Mol ratio deuterated/undeuterated compound in the final solution. For details on the calculation of this ratio and the response factor of deuterated compounds, see the Supporting Information. [f] The ratio $d_0/d_5/d_{10}$. Note that the statistical ratio in the absence of any isotope effect is 1:2:1.

although, at this stage, we could not detect any product clearly assignable to such a competitive reaction. The equation describing the best fit to all other points ($R^2 = 0.985$, Figure 3) has the form:

$$\log(\text{indole selectivity \%}/100) = -0.292\sigma + 0.368\sigma_{JJ\bullet} - 0.529$$

While the absolute values of the coefficient are somewhat arbitrary, it is important that the coefficients associated with the two constants are comparable in magnitude, indicating that both polar and radical stabilization effects are relevant in determining the selectivity.

An analogous data analysis was attempted with the results in Table 2, but no clear correlation could be obtained. However, it should be considered that alkynes can coordinate to palladium, and the role of such a complex (intermediate or dead branch of the catalytic cycle) is not known at this stage. That the alkyne plays a role before the rate-determining activation of the nitroarene is indicated by the fact that the conversion of the latter depends on both the alkyne amount and its identity (see also later).

To investigate whether the cyclization step was important in determining the selectivity of the reaction, we investigated the isotopic effect running three parallel reactions employing either pure $C_6H_5NO_2$ and $C_6D_5NO_2$ or a 1:1 mixture of the two as substrates. Results are reported in Table 3. Close to the experimental error, both the nitroarene conversion and the selectivity in indole were the same in all cases. Even in the competition experiment, an isotope effect of around 1.08−1.15 can explain the data. This is consistent with a secondary deuterium effect but is inconsistent with a primary isotopic effect, indicating that the selectivity-determining step is not the cyclization step.

We can now draw a tentative reaction scheme on the basis of the supposition, following the work by Nicholas et al.,[6,7] that the reaction between the nitrosoarene and the alkyne occurs outside the coordination sphere of the metal (Scheme 2).

By an analogy with the reactions with olefins, the nitrosoarene should interact reversibly with the alkyne to give an intermediate having a polarized diradical character.[26] Only two of several possible resonance structures are depicted in the scheme. Note that this intermediate (**A**) has been drawn with a linearly arranged benzylic carbon atom because this is the geometry that has been determined to be most stable both for α-styryl cations (by theoretical calculations[31]) and α-styryl radicals (by EPR[32] and fluorescence spectroscopy[33]). Cyclization would give the hydroxyindole, which, in the presence of CO and the catalyst, is reduced to indole. Alternatively, the nitrosoarene can react with itself to give, in the presence of CO and the catalyst, the azoxyarene, a well-precedented reaction.[2]

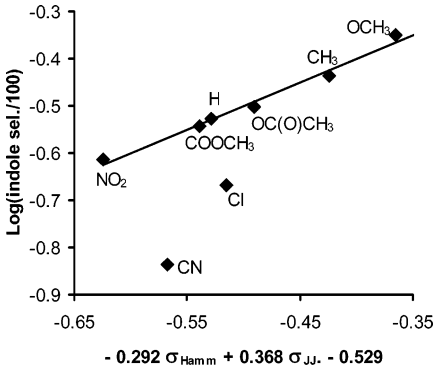
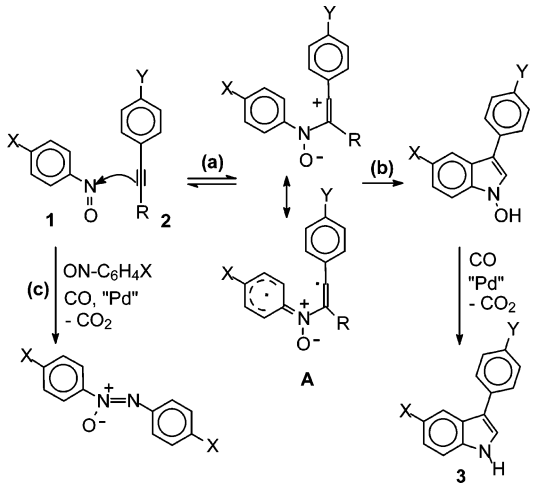


FIGURE 4. Plot of log(indole selectivity %/100) vs the best multivariate combination of Hammett σ and $\sigma_{JJ\bullet}$ constants for the data in Table 1 ($R^2 = 0.985$). The data for **1b** and **1d** are shown but were not included in the calculation of the best fit.

SCHEME 2



The selectivity should be higher if steps (a) and (b) are fast with respect to (c). Step (b) must be fast because no isotope effect is observed. The radical character of the intermediate adducts nicely explains the need for an aryl group on the alkyne, the regioselectivity (the aryl ring stabilizes charges or a radical in the α position), and also the beneficial role of radical-stabilizing groups on the nitroarene. On the other hand, the polarization that can be inferred from the sign of the Hammett σ coefficient of the plot in Figure 4 is opposite to that depicted in the scheme and would place a negative charge on the benzylic carbon. Such a polarization is unlikely unless the intermediate is bound to palladium through that carbon atom.

To gain more information on the cyclization step, we performed some stoichiometric experiments. Since palladium(0) carbonyl complexes, such as those that are likely formed by reduction of $[Pd(phen)_2][BF_4]_2$, under the reaction conditions are not stable, we employed Pd(phen)(dba) as a starting material.

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We have previously reported that nitrosobenzene reacts with this complex to give an insoluble and apparently polymeric compound[34] that cannot be employed as a model for any intermediate in the indole synthesis. During this work, we tried to isolate an alkyne complex of the kind Pd(phen)(alkyne) (alkyne = **2a**, **2b**, or **2e**) by the reaction of Pd(phen)(dba) with the alkyne in THF. An immediate reaction was observed in all cases and with different reagent ratios, but insoluble and apparently polymeric products were always observed. It should be noted that only very few palladium−alkyne complexes have been isolated in the solid state[35,36] or even characterized in solution and none of them having only nitrogen ligands. Thus, although reactivity data suggest an involvement of the metal even in the cyclization step, the exact mechanism by which this occurs cannot be individuated at the moment.

Conclusions

In conclusion, we have shown that a palladium catalyst is more convenient than the reported ruthenium one for the intermolecular condensation of nitroarenes and alkynes to afford indoles. Several functional groups are tolerated on the nitroarene, except for bromide and activated chloride. The presence of a C−Br bond is especially deleterious, and brominated compounds should not be present, even in trace amounts. As far as the alkyne is concerned, only arylalkynes gave the indole among the substrates tested, and the aryl ring was selectively found at the 3-position of the indole. Some mechanistic features have been explained, and more work is in progress to clarify the remaining ones and to improve the selectivity of the reaction.

Experimental Section

Catalytic Reactions. In a typical reaction, the reagents (see Tables 1 and 2) were quickly weighed in a glass liner. The liner was placed inside a Schlenk tube with a wide mouth under dinitrogen, frozen at − 78 °C with dry ice, evacuated, and filled with dinitrogen, after which the solvent was added. After the solvent was also frozen, the liner was closed with a screw cap having a glass-wool-filled open mouth, which allows for gaseous reagents exchange, and rapidly transferred to a 200-mL stainless steel autoclave with magnetic stirring. The autoclave was then evacuated and filled with dinitrogen three times. CO was then charged at room temperature at the required pressure, and the autoclave was immersed in an oil bath preheated at the required temperature. Other experimental conditions are reported in Table 1. At the end of the reaction, the autoclave was cooled with an ice bath and vented, and the products were analyzed by gas chromatography (naphthalene as an internal standard) to determine the nitroarene conversion and, in the case of the reactions involving nitrobenzene and phenylacetylene, the amounts of **3aa**, aniline, azobenzene, and azoxybenzene formed. Then 2,4-dinitrotoluene was added as an internal standard, and the solution was evaporated in vacuo. The residue was dissolved in $CDCl_3$ and analyzed by ^1H NMR using a delay of 10 s. The obtained value for the amount of indole formed was corrected for the small amount of solution withdrawn for the gas chromatographic analysis. The reactions in Tables 2 and 3 were performed in a similar way, but, in this case, three 10 mm wide × 40 mm high test tubes were employed instead of the glass liner, each having a miniature glass-wool-filled screw cap similar to the one of the larger liner. The three test tubes were located in the holes of an aluminum block designed to fit the autoclave. Other operations were analogous to the ones described above except that stock solutions of the catalyst, the ligand, and the nitroarene were prepared, and the reagent amounts were measured by volume to avoid the errors in weighing very small amounts of materials. Because the catalyst was not completely soluble at rt in some cases, the suspension was irradiated with ultrasounds immediately before the withdrawal to homogeneously disperse the catalyst. Stock solutions were also employed in the experiments with deuterated nitrobenzene. For the competitive experiment, equal volumes of stock solutions (0.5 mL each) in $PhNO_2$ and $PhNO_2$-d_5 were added.

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Supporting Information Available: General Experimental Section; details on the quantification of deuterated compounds; characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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