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2-Substituted-3-acylindoles through the Palladium-Catalysed Carbonylative Cyclization of 2-Alkynyltrifluoroacetanilides with Aryl Halides and Vinyl Triflates

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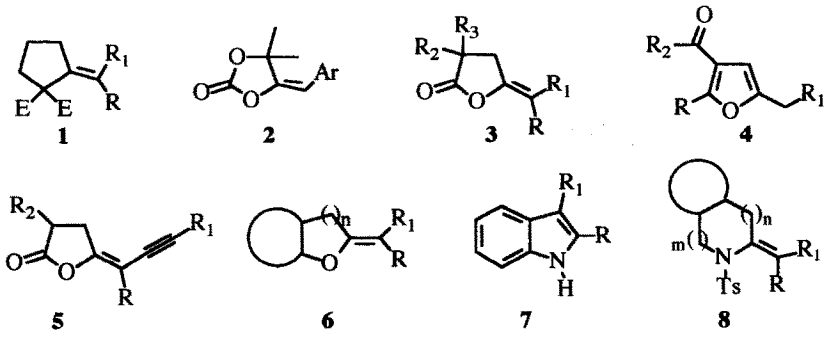
Abstract: *The palladium-catalysed reaction of readily accessible 2-alkynyltrifluoroacetanilides with aryl halides and vinyl triflates under a carbon monoxide atmosphere (1 or 7 atm) and in the presence of potassium carbonate produces 2-substituted-3-acyl indoles in fair to good yield. The acidity of the nitrogen-hydrogen bond proved to be of primary importance for the success of the reaction. The methodology has been applied to the synthesis of pravadoline, a drug that shows analgesic activity against postoperative pain in man.*

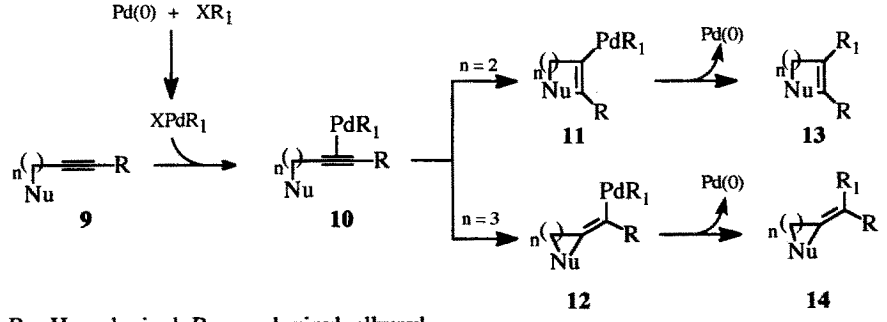
Introduction

The recently discovered ability of the *in situ* generated σ-vinyl-, σ-aryl-, and σ-alkynylpalladium complexes to activate carbon-carbon triple bonds towards intramolecular nucleophilic attack is emerging more and more as a valuable tool in organic synthesis. The reaction, only partly related to the cyclization of alkynes containing nucleophiles near the carbon-carbon triple bond catalysed by palladium dihalides or dicarboxylates,[1,2,3] provides a unique procedure for the functionalization of internal and terminal alkynes. It allows in fact the stereo- and regioselective addition of a nucleophile and of a vinyl, aryl, or alkynyl unit to the carbon-carbon triple bond leading to the formation of hetero- and carbo-cycles. A variety of these transformations involving alkynes containing carbon, oxygen, and nitrogen nucleophiles has been published.

Alkynes containing carbon nucleophiles have been reported to react with aryl halides giving rise to carbocyclic derivatives **1**.[4] A number of oxygen-containing heterocycles have been prepared from alkynes containing oxygen nucleophiles. The monoalkynylcarbonate generated *in situ* from sodium 2-methyl-3-butyn-2-olate and carbon dioxide has been described to react with aryl halides to give (*E*)-5-arylidene-4,4-dimethyl-1,3-dioxolan-2-ones **2**.[5] Pentynoic acids and 2-propargyl-1,3-dicarbonyl compounds, have been reacted with vinyl triflates and aryl halides to give (*E*)-γ-alkylidene-γ-butyrolactones **3**[6] and 2,3,5-trisubstituted furans **4**,[7] respectively. Pentynoic acids have been also reported to react with 1-bromo-1-alkynes to afford (*E*)-γ-alkynylidene-γ-butyrolactones **5**,[8] so far the only cyclization based on a nucleopalladation step promoted by σ-alkynylpalladium complexes. 2-Alkylidenetetrahydrofurans **6** have been prepared from the reaction of acetylenic alcohols[9] with aryl halides. Alkynes containing nitrogen nucleophiles such as 2-alkynyltrifluoroacetanilides and tosylamides have been converted into 2,3-disubstituted indoles **7**[10] and 2-alkylidenepyrrolidines or -piperidines **8**,[11] respectively.



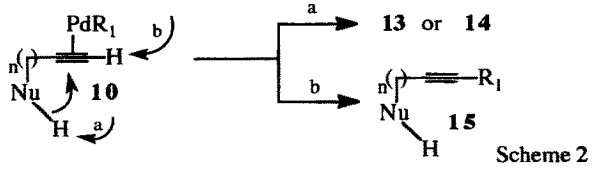
Mechanistically, the palladium-catalysed *exo-dig* or *endo-dig* cyclization of compounds **9** has been proposed to proceed through a) generation of the π-alkynylpalladium complex **10**, b) intramolecular nucleophilic attack generating the σ-vinylpalladium intermediates **11** or **12**, c) reductive elimination giving rise to the cyclic derivatives **13** or **14** and regenerating the palladium(0) catalyst (Scheme 1). Apparently, anionic nucleophiles are needed to allow the intramolecular nucleophilic attack on the carbon-carbon triple bond coordinated to palladium. Indeed, whereas π-alkynylpalladium complexes derived from palladium dihalides or dicarboxylates have been extensively reported to undergo intramolecular nucleophilic attack by hydroxy,[1] amino,[1d,2] and amido[2d,3] groups, only cyclizations based on the nucleophilic attack of anions on the carbon-carbon triple bond of the π-alkynylpalladium complexes **10** have been described. The nature and the strength of the base are two of the main factors determining the reaction outcome.[7-10]



R = H, aryl, vinyl; R_1 = aryl, vinyl, alkynyl
Nu = $E_1E_2C^-$, O^-, COO^-, TsN^-, CF_3CON^-

Scheme 1

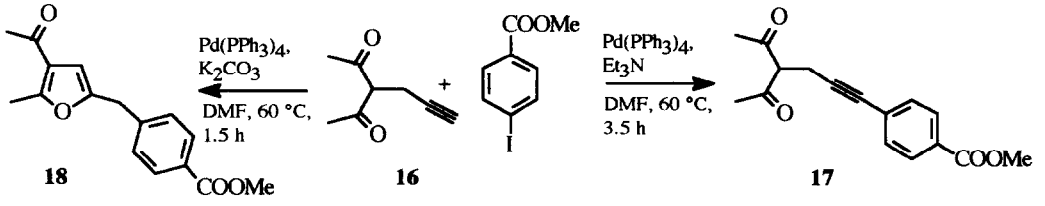
With 1-alkynes (R = H), the formation of the π-palladium complex **10** may result in the activation towards intramolecular nucleophilic attack on the coordinated carbon-carbon triple bond leading to cyclic



Scheme 2

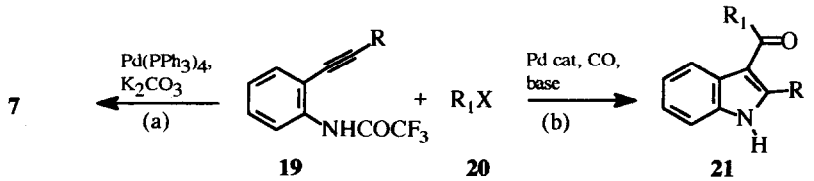
derivatives **13** or **14** (Scheme 2a) and/or in the intermolecular base attack on the terminal carbon-hydrogen bond leading to the coupling derivative **15** (Scheme 2b).[12]

The cyclization/coupling balance is strongly dependent on the nature of the added base. For example, in the presence of triethylamine 3-propargyl-2,4-pentandione **16** reacts with methyl 4-iodobenzoate producing the coupling product **17** (55% yield) whereas in the presence of K_2CO_3 the furan derivative **18** is isolated in 56% yield (Scheme 3).[7]



Scheme 3

Since we are currently engaged in a program devoted to the use of palladium catalysis in the development of new routes to indole derivatives[2c,10,13] we decided to investigate the possible extension of the methodology developed for the preparation of 2,3-disubstituted indoles **7**[10] (Scheme 4a) to the synthesis of 2-substituted-3-acylindoles **21** (Scheme 4b). 3-Acylindoles have been reported to be important therapeutic agents[14] and useful intermediates for the preparation of pyridocarbazole alkaloids.[15]



X = I, OTf
R = alkyl, vinyl, aryl; R_1 = vinyl, aryl

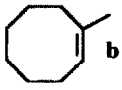
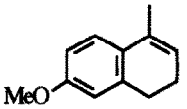
Scheme 4

In this paper we report the results of this study.

Reaction of 2-Alkynyltrifluoroacetanilides with Aryl Halides

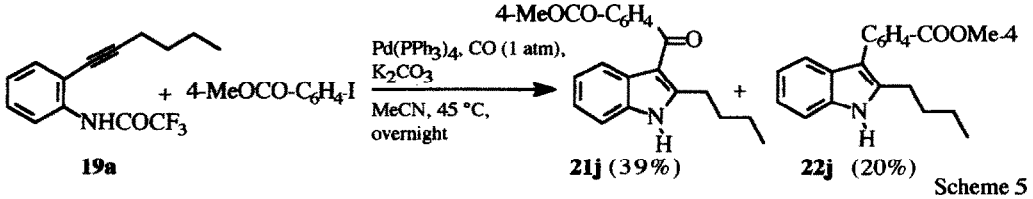
Based on the results obtained in the palladium-catalysed synthesis of 2,3-disubstituted indoles,[10] we initially examined the reaction of 2-(hex-1-ynyl)trifluoroacetanilide **19a** with 4-methoxyphenyl iodide in the presence of K_2CO_3 and $Pd(PPh_3)_4$ in acetonitrile under a balloon of carbon monoxide at 45 °C. Under these conditions the indole derivative **21a** was isolated in 83% yield (Table 1, entry a) whereas the use of AcOK and $KHCO_3$ met with failure (Table 1 entries b and c). The same conditions were successfully utilised for the reaction of other 2-alkynyltrifluoroacetanilides with aryl halides (Table 1, entries e, h-l). The use of $Pd(OAc)_2(PPh_3)_2$ as the catalyst produced good results as well (Table 1, entry d).

Table 1. Palladium-Catalysed Synthesis of 2-Substituted-3-acylindoles **21** from 2-Alkynyltrifluoroacetanilides **19** and Aryl Halides.[a]

entry	2-alkynyltrifluoroacetanilide **19** R	aryl halide **20**	catalyst	2-substituted-3-acylindole **21** (yield %)[b]	2-substituted-3-arylindole **22** (% yield)[b]
a	$-CH_2(CH_2)_2CH_3$ **a**	4-MeO-C_6H_4-I	$Pd(PPh_3)_4$	83 **a**	
b	"	"	"	7 "[c]	
c	"	"	"	- "[d]	
d	"	"	$Pd(OAc)_2(PPh_3)_2$	77 "	
e	"	4-MeCONH-C_6H_4-I	$Pd(PPh_3)_4$	72 **b**[e]	
f	"	4-Cl-C_6H_4-I	$Pd(dba)_2/P(o\text{-tol})_3$[h]	39 **c**[e]	8
g	"	"	$Pd(PPh_3)_4$	14 "[f,g]	traces
h	 **b**	4-MeO-C_6H_4-I	$Pd(PPh_3)_4$	77 **d**	
i	Ph **c**	3-Me-C_6H_4-I	"	57 **e**	
j	"	4-MeO-C_6H_4-I	"	60 **f**	
k	Me **d**	"	"	73 **g**	15
l	 **e**	4-Me-C_6H_4-I	"	73 **h**	8
m	 **f**	3-F-C_6H_4-I	"	43 **i**	17
n		"	"	64 "[f,g]	
o		"	$Pd(dba)_2/P(o\text{-tol})_3$[h]	52 "[e]	5

[a] Unless otherwise stated, reactions were carried out in MeCN overnight at 45 °C, under a balloon of carbon monoxide, using the following molar ratios: **19**: aryl halide: $Pd(PPh_3)_4$: K_2CO_3 = 1: 1.2: 0.05: 5. [b] Yields refer to single runs and are for pure, isolated products. [c] $KHCO_3$ was used as the base (**19a** was recovered in 84% yield). [d] AcOK was used as the base (**19a** was recovered in 81% yield). [e] 40 h. [f] In a stainless steel bomb, under a seven atmosphere pressure of carbon monoxide. [g] In commercially available anhydrous MeCN. [h] Pd/P = 1/4.

However, when the reaction was applied to aryl halides containing electron-withdrawing groups, the yields were unsatisfactory. As an example, reacting 2-(hex-1-ynyl)trifluoroacetanilide with methyl 4-iodobenzoate led to only partial conversion of the starting material and the corresponding acylindole **21j** was isolated in 39% yield (Table 2, entry a). In addition, competitive non-carbonylative cyclization was found to be a significant side reaction and 3-(4-carbomethoxy)-phenylindole **22j** was obtained in 20% yield (Scheme 5).



Scheme 5

The possible influence of ligands and carbon monoxide pressure on the reaction outcome was then investigated. Readily available $Pd(dba)_2$[16] (dba = dibenzylidene acetone),[17,18] containing an easily displaced ligand, was used for these experiments. The catalysts were prepared *in situ* from $Pd(dba)_2$ and the selected

phosphine ligand, usually in a 1/ 4 ratio (1/ 2 with bidentate ligands). We are uncertain, however, about the nature of the active catalyst nor we have investigated the effect of the Pd/P ratio on the course of the reaction. The **21j/22j** ratio was found to increase to about 3 in the presence of electron-donating ligands such as P(*p*-tol)$_3$ or P(4-MeO-C$_6$H$_4$)$_3$ (Table 2, entries c and d) but the acylindole was isolated in low to moderate yield.

The use of bidentate ligands led to disappointing results, at least from a synthetic point of view. With dppf [bis-(triphenylphosphino)ferrocene] and dppp [bis-(triphenylphosphino)propane] the starting alkyne was recovered in high yield (Table 2, entries e-h) whereas the utilization of dppe [bis-(triphenylphosphino)ethane] resulted in a higher conversion of **19a** but the **21j/22j** ratio decreased to about 0.61 (Table 2, entry i). As expected, the ratio between **21j** and **22j** increased notably (to about 6) by carrying out the reaction under a seven atmosphere pressure of carbon monoxide (Table 2, entry j). Nevertheless, only a moderate conversion of the starting material was observed and **21j** was isolated in low yield. Searching for better reaction conditions and based on the idea that an anhydrous medium could prevent possible competitive hydrolysis of acylpalladium intermediates, the use of anhydrous acetonitrile (commercially available; packaged under nitrogen, over molecular sieves) was attempted. In the effect, a marked improvement both in the conversion of **19a** and in the **21j/22j** ratio was observed (Table 2, entry k). Other 3-acylindoles have been therefore prepared from 2-alkynyltrifluoroacetanilides and aryl halides containing electron-withdrawing groups (Table 1, entries g and n) and vinyl triflates (Table 3) in this solvent. Interestingly, the utilization of Pd(dba)$_2$/P(*o*-tol)$_3$ in acetonitrile and under a balloon of carbon monoxide led to the isolation of **21j** in a yield comparable to the one obtained with Pd(PPh$_3$)$_4$, anhydrous acetonitrile, and seven atmosphere of carbon monoxide (Table 2, entry b). However, no constant, distinctive advantages have been observed when these last conditions have been applied to other aryl halides containing electron-withdrawing groups (Table 1; compare entry f with entry g and entry n with entry o) or to vinyl triflates (Table 3; compare entry j with entry k).

Table 2. Palladium-Catalysed Synthesis of 2-Butyl-3-(4-carbomethoxybenzoyl)-indole **21j** from 2-Alkynyltrifluoroacetanilide **19a** and Methyl 4-Iodobenzoate.[a]

entry	P_{CO} (atm)	catalyst (palladium: ligand ratio)	recovered **19a** (% yield)[b]	**21j** (% yield)[b]	**22j** (% yield)[b]
a	1	Pd(PPh$_3$)$_4$	36	39	20
b	1	Pd(dba)$_2$/P(*o*-tol)$_3$ (1: 4)	9	68	15
c	1	Pd(dba)$_2$/P(*p*-tol)$_3$ (1: 4)	35	40	15
d	1	Pd(dba)$_2$/P(4-MeO-C$_6$H$_4$)$_3$ (1: 4)	35	25	8
e	1	Pd(dba)$_2$/dppf (1: 2)	76	-	2
f	1	Pd(dba)$_2$/dppf (1: 1)	81	-	5
g	1	Pd(dba)$_2$/dppp (1: 2)	89[c]	-	-
h	1	Pd(dba)$_2$/dppp (1: 1)	66	5	8
i	1	Pd(dba)$_2$/dppe (1: 2)	12	28	46
j	7	Pd(PPh$_3$)$_4$	51	31	5
k	7	Pd(PPh$_3$)$_4$	9	64[d]	9
l	7	Pd(dba)$_2$/P(*o*-tol)$_3$ (1: 4)	80	10	traces

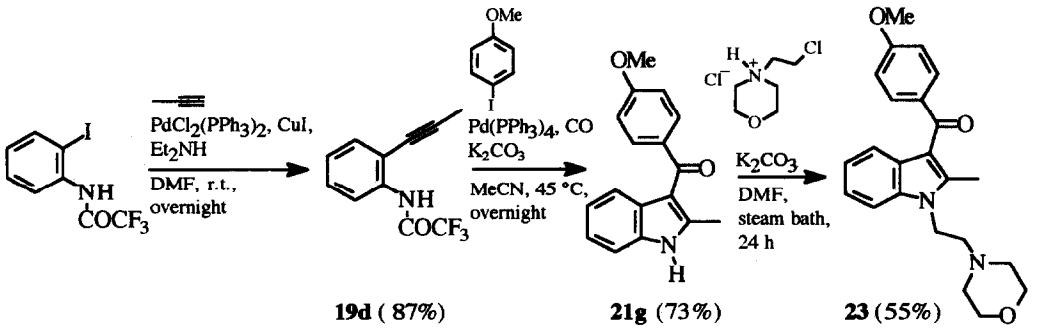
[a] Unless otherwise stated, reactions were carried out in MeCN overnight, at 45 °C, using the following molar ratios: **19a**: methyl 4-iodobenzoate: Pd cat = 1: 1.2: 0.05.[b] Yields refer to single runs and are for pure, isolated products.[c] Methyl 4-iodobenzoate was recovered in 84% yield.[d] In commercially available anhydrous MeCN.

To sum up, the use of Pd(PPh$_3$)$_4$ or Pd(OAc)$_2$(PPh$_3$)$_2$ in acetonitrile, under a balloon of carbon monoxide, can give good results in many cases. With aryl halides containing electron-withdrawing groups, the use of anhydrous acetonitrile and a higher pressure of carbon monoxide is needed. With these substrates, the utilization of Pd(dba)$_2$/P(*o*-tol)$_3$ in acetonitrile, under a balloon of carbon monoxide, can provide an alternative, simpler procedure but its effectiveness is to be evaluated each time.

An attempt was made to extend the reaction to the preparation of 2-unsubstituted-3-acylindoles. However, reacting 2-ethynyltrifluoroacetanilide with 4-methoxyphenyl iodide under usual conditions produced a complex reaction mixture that was not further analysed.

The use of acyl chlorides as precursors of acylpalladium intermediates was also examined but direct nitrogen acylation appears to be faster than the desired palladium-catalysed reaction. Treatment of 2-(hex-1-ynyl)trifluoroacetanilide with benzoyl chloride (K_2CO_3, anhydrous acetonitrile, room temperature, 6 h) both in the presence and in the absence of $Pd(PPh_3)_4$ gave 2-(hex-1-ynyl)benzanilide in 52 and 51% yield, respectively.

The methodology was applied to the synthesis of pravadoline **23**, an indole derivative designed as a nonacidic analogue of non-steroidal anti-inflammatory drugs (NSAIDs) (Scheme 6).[19] The last step was carried out according to the literature.[14a]



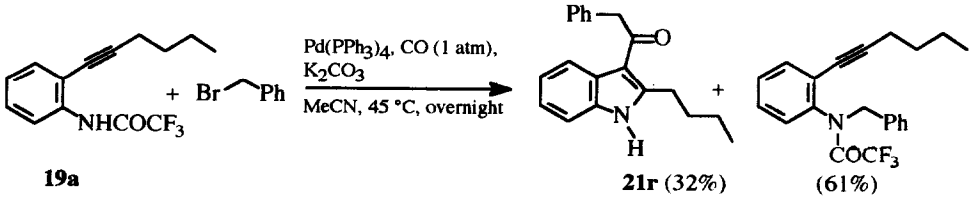
Scheme 6

Reaction of 2-Alkynyltrifluoroacetanilides with Vinyl Triflates

Vinyl triflates have been reacted with 2-alkynyltrifluoroacetanilides under a balloon of carbon monoxide in the presence of $Pd(PPh_3)_4$ producing the corresponding acylindoles in moderate to good yield (Table 3). In this case too, anhydrous acetonitrile gave the best results (Table 3, compare entry a with entry b). The use of other solvents proved to be unsatisfactory (Table 3, entries c and d). Increasing the pressure of carbon monoxide did not produce better results, at least in the case examined (Table 3; compare entry f with entry g). Some of the vinyl triflates we tested, however, afforded complex reaction mixtures containing small amounts or traces, if any, of the expected acylindoles.[20]

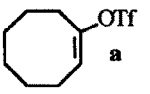
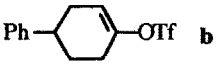
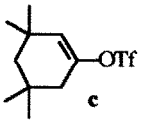
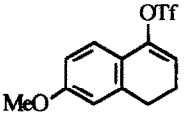
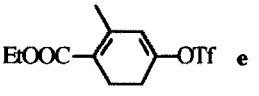
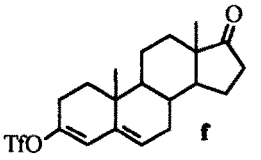
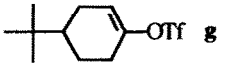
Reaction of 2-Alkynyltrifluoroacetanilides with Benzyl Halides

Benzyl bromide was used as a model system and its reaction with **19a** was carried out in the presence of $Pd(PPh_3)_4$ under a balloon of carbon monoxide in anhydrous acetonitrile. The corresponding acylindole **21r** was isolated in only 32% yield. N-Benzylation of the starting alkyne was found to be faster than the palladium-catalysed carbonylative cyclization[21] and 2-(hex-1-ynyl)-N-benzyl-trifluoroacetanilide was isolated in 61% yield (Scheme 7).

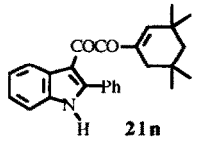


Scheme 7

Table 3. Palladium-Catalysed Synthesis of 2-Substituted-3-acylindoles **21** from 2-Alkynyltrifluoroacetanilides **19** and Vinyl Triflates.[a]

entry	2-alkynyltrifluoroacetanilide **19** R	vinyl triflate **20**	2-substituted-3-acylindole **21** (yield %)[b]	2-substituted-3-vinylindole **22** (% yield)[b]
a	$-CH_2(CH_2)_2CH_3$ **a**	 **a**	60 **k**	
b	"		41 "[c]	
c	"		7 "[d]	
d	"		16 "[e]	
e	"	 **b**	52 **l**	
f	Ph **c**	 **c**	68 **m**	23
g	"		68 "[f]	traces
h	"	 **d**	-	
i	"	 **e**	-	
j	3-Me-C_6H_4- **g**	 **f**	64 **p**	25
k	"		8 "[g]	7
l	Ph **c**	 **g**	45 **q**	

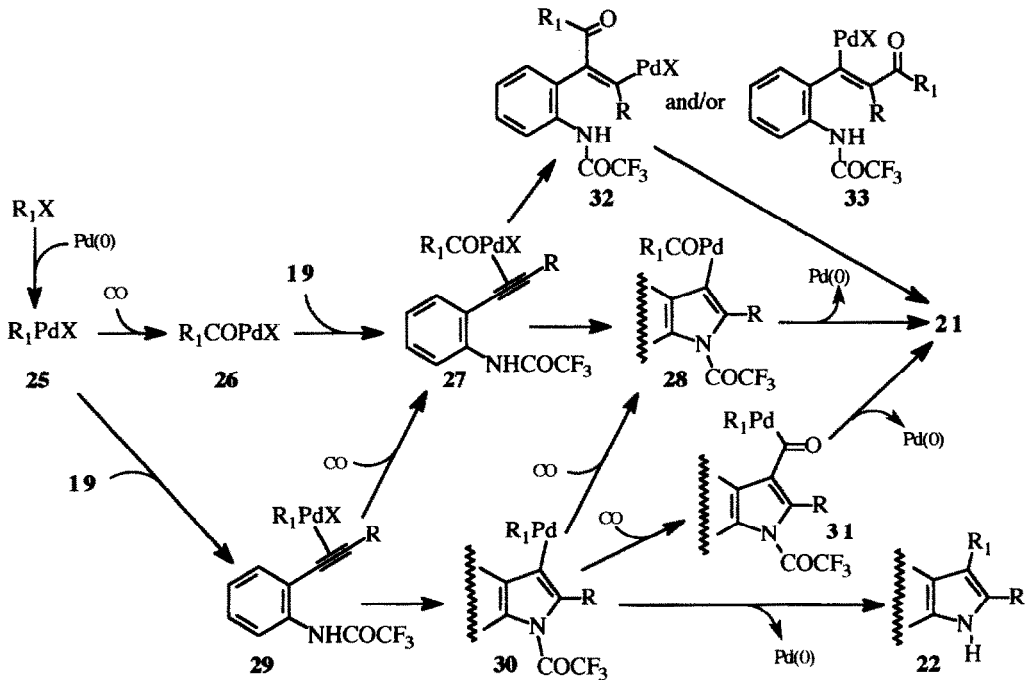
[a] Unless otherwise stated, reactions were carried out overnight at 45 °C in commercially available anhydrous MeCN, under a balloon of carbon monoxide, using the following molar ratios: **19**: vinyl triflate: $Pd(PPh_3)_4$: K_2CO_3 = 1: 1.2: 0.05: 5.[b] Yields refer to single runs and are for pure, isolated products.[c] In MeCN.[d] In commercially available anhydrous DMSO.[e] In commercially available anhydrous N-methylpyrrolidone.[f] Under a seven atmosphere of carbon monoxide. Under these conditions the 1,2-dicarbonyl derivative **21n** was isolated in 13% yield. [g] In the presence of $Pd(dba)_2$/P(*o*-tol)$_3$ = 1/4. The starting alkyne was recovered in 75% yield.



21n

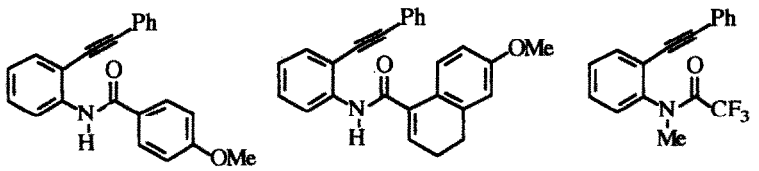
Discussion

The cyclization of 2-alkynyltrifluoroacetanilides **19** to 2-substituted-3-acylindoles **21** can be rationalized according to the following sequence: a) formation of the oxidative addition complex **25**, b) carbonylation of **25** to give the σ-acylpalladium intermediate **26**, c) generation of the π-alkynylpalladium complex **27**, d) intramolecular nucleophilic attack of the nitrogen anion on the carbon-carbon triple bond to afford **28**, and e) reductive elimination of a Pd(0) species (Scheme 8). According to this view, the activation of the carbon-carbon triple bond towards nucleophilic attack is promoted by σ-acylpalladium complexes.



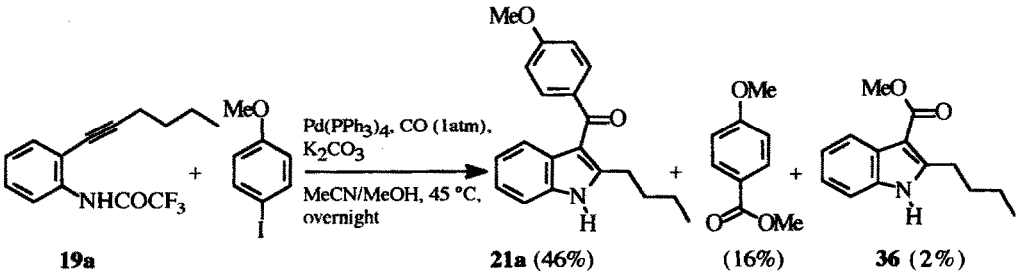
Scheme 8

Alkynes containing free amino groups fail to produce cyclic derivatives.[10] This observation supports the notion that a more reactive nitrogen anion is needed to allow the cyclization reaction. No indole derivative was isolated from the reaction of 2-phenylethynylaniline with 4-methoxyphenyl iodide or 6-methoxy-3,4-dihydro-1-naphthyl triflate under usual conditions. With 4-methoxyphenyl iodide, 2-phenylethynylaniline was recovered in 75% yield along with the amide **34** (19% yield) whereas the acylpalladium complex derived from 6-methoxy-3,4-dihydro-1-naphthyl triflate was found to be more susceptible to the nucleophilic attack of the nitrogen atom and the amide **24** was isolated in 66% yield. The starting alkyne was recovered in 20% yield. The recovery of N-methyl-2-phenylethynyltrifluoroacetanilide **35** in 89% yield from its reaction with 4-methoxyphenyl iodide and no formation of indole derivatives in this case too, provides further evidence that the carbon-carbon triple bond in the π-palladium complex **27** is subject to nucleophilic attack by the anionic nitrogen of the trifluoroacetamido group.



The isolation of the 2,3-disubstituted indoles **22** clearly shows that a non-carbonylative pathway, most probably based on the intermediacy of the π-alkynylpalladium complex **29** and of the σ-vinylpalladium complex **30**, is operating as well. On the other hand, this mechanism has been supposed to account for the formation of 2,3-disubstituted indoles in our palladium-catalysed reaction of 2-alkynyltrifluoroacetanilides with vinyl triflates and aryl halides in the absence of carbon monoxide.[10] Under an atmosphere of carbon monoxide, however, it is reasonable to suppose that the palladium complexes **29** and **30** can be converted into the corresponding carbonylated complexes **27** and **28**, thus contributing to the formation of the target acylindoles. It is also to note that the σ-vinylpalladium complex **30** can produce both **28** and **31**, depending upon the carbon-palladium bond cleaved during the insertion process, and that the σ-vinylpalladium complex **31** can afford **21** through reductive elimination of a Pd(0) species.

To shed some light on the reaction mechanism, 2-hexynyltrifluoroacetanilide **19a** was reacted with 4-methoxyphenyl iodide under usual conditions, in the presence of methanol as the trapping agent for acylpalladium intermediates. Trapping **26**, **27**, and **28** with methanol would produce methyl 4-iodobenzoate. Its formation would be in agreement with their involvement in the sequence leading to **21** from **26**. In addition, the acylpalladium complex **31** is expected to generate a 3-methoxycarbonyl indole derivative which would provide a considerable support to the view that also the palladium complexes **29**, **30**, and **31** lie on a product-forming reaction path. This was found to be the case and, although in very low yield, 2-*n*-butyl-3-methoxycarbonyl indole **36** was isolated from the reaction mixture together with methyl 4-iodobenzoate and 2-butyl-3-(4-methoxybenzoyl)-indole **21a** (Scheme 9). The structure of **36** was determined by spectroscopic analysis and confirmed by preparation of an authentic specimen through the palladium-catalysed reaction of 2-(hex-1-yn-1-yl)-aniline with carbon monoxide in methanol.[22]



Scheme 9

Another possible reaction pathway leading to 2-substituted-3-acylindoles involves the σ-vinylpalladium complex **32**. The addition intermediate **32** can in fact produce **21** through the conjugate addition of the nitrogen anion to the α,β-enonic system followed by the reductive elimination of a Pd(0) species. Available data do not allow to support or rule out this parallel mechanism. However, addition intermediates of this kind have been supposed to be involved in the recently reported palladium-catalysed synthesis of 2-alkyl-3-acyl-5-

arylfurans from 1-aryl-2-alkyn-1-ones and aryl iodides under an atmosphere of carbon monoxide.[23] Clearly the contribution of this mechanism to the formation of acylindoles depends, *inter alia*, on the regioselectivity of the carbopalladation step. On this point, and to the extent that the results obtained in our hydroarylation and hydrovinylation reactions on alkynes[24] can be assumed as a model, it can be added that the formation of addition σ-vinylpalladium complexes from a variety of alkynes and organopalladium complexes have been found to be controlled mainly by steric and coordinating factors. Electronic effects may also be at work in the carbopalladation of carbon-carbon triple bonds[25] but they seem to control effectively the regiochemistry of the reaction only in acetylenic systems bearing strongly electron-withdrawing groups.[23]

In conclusion, the palladium-catalysed reaction presented herein constitutes a novel route to the interesting class of 2-substituted-3-acylindoles. The starting 2-alkynyltrifluoroacetanilides are readily accessible and the cyclization reaction is very easy to perform, occurs under mild conditions, and should probably tolerate a variety of functional groups. Our method should complement well the usual acylation of the indole skeleton with acyl halides as well as the acylation reaction based on the generation of anionic species from 3-halo derivatives.

Experimental section

Melting points were determined with a Büchi apparatus and are uncorrected. All the starting materials, $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(OAc)_2(PPh_3)_2$, ligands, amines, salts, and solvents (anhydrous solvents included) are commercially available and were used as purchased, without further purification. $Pd(dba)_2$ was prepared according to reference 16. Vinyl triflates **20a**,**c-e**,[12] **20b**,**f**,[6] and **20g**[26] were prepared according to reference 27 and purified by flash chromatography on silica gel eluting with *n*-hexane/EtOAc mixtures. Methyl 4-iodobenzoate[28] was prepared according to the procedure given in ref 29 for the synthesis of methyl 2-iodobenzoate and purified by chromatography on silica gel eluting with *n*-hexane/EtOAc (90/10 v/v). Palladium-catalysed conversion of 2-alkynyltrifluoroacetanilides **19** into 2-substituted-3-acylindoles **21** was carried out on a 0.2 - 2.0 mmol scale. The products were purified by flash chromatography on silica gel eluting with *n*-hexane/EtOAc mixtures.

^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra ($CDCl_3$; TMS as internal standard) were recorded with a Bruker AC 200 E spectrometer. IR spectra (KBr, unless otherwise indicated) were recorded with a Perkin-Elmer 683 spectrometer. MS spectra were recorded on a spectrometer HP 59970 workstation formed by an HP 5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP 5970 mass detector.

General Procedure for the Preparation of 2-Alkynyltrifluoroacetanilides (19).

From 2-Iodotrifluoroacetanilide (Procedure A). 2-Phenylethynyltrifluoroacetanilide (19c). To a solution of 2-iodotrifluoroacetanilide (1.22 g, 3.87 mmol) in DMF (3 mL) were added phenylacetylene (0;51 mL, 4.65 mmol), diethylamine (2.5 mL), $Pd(OAc)_2(PPh_3)_2$ (0.029 g, 0.038 mmol), and CuI (0.015 g, 0.077 mmol). The reaction mixture was stirred at room temperature under nitrogen for 7 h and poured in a separatory funnel containing 0.1 N HCl and diethyl ether. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with a 97/3 *n*-hexane/EtOAc mixture to afford 0.82 g (73% yield) of **19c**: mp 94-96 °C; IR 3350, 2220, 1710 cm^{-1}; ^1H NMR δ 8.88 (bs, 1 H), 8.36 (d, J= 8 Hz, 1 H), 7.60-7.36 (m, 7 H), 7.20 (dt, J = 8 Hz, J = 1,2 Hz, 1 H); ^{13}C NMR δ 154.4 (q, J = 37 Hz), 136.1, 131.7, 131.5, 129.8, 129.3, 128.7, 125.5, 121.7, 119.6, 115.8 (q, J= 289 Hz), 113.5, 98.1, 82.9; MS *m/e* (relative intensity) 289 (M^+, 100), 220 (40), 192 (32). Anal. Calcd. for $C_{16}H_{10}F_3ON$: C, 66.44; H, 3.48; N, 4.84. Found: C, 66.94; H, 3.71; N, 4.42.

From 2-Ethynyltrifluoroacetanilide (Procedure B). 2-(Cyclooct-1-enyl)ethynyltrifluoroacetanilide (19b). To a stirred solution of 2-ethynyltrifluoroacetanilide (0.153 g,

0.72 mmol) in DMF (0.5 mL) were added diethylamine (2 mL), cyclooct-1-enyl triflate (0.185 g, 0.72 mmol), $Pd(PPh_3)_4$ (0.008 g, 0.007 mmol), and CuI (0.003 g, 0.015 mmol). The reaction mixture was stirred at room temperature under nitrogen for 4.5 h and worked-up as usual. The residue was purified by flash chromatography on silica gel eluting with a 97/3 *n*-hexane/EtOAc (v/v) mixture to give 0.212 g (92% yield) of **19b**: mp 87-9 °C; IR 3300, 2180, 1700 cm^{-1}; ^1H NMR δ 8.82 (bs, 1 H), 8.34 (d, J = 7.8 Hz, 1 H), 7.48-7.32 (m, 2 H), 7.16 (dt, J = 7.6 Hz, J = 1.2 Hz, 1 H), 6.28 (t, J = 8.4 Hz, 1 H), 2.44-2.17 (m, 4 H), 1.60 (bs, 8 H); ^{13}C NMR δ 154.4 (q, J = 37 Hz), 140.2, 135.9, 131.4, 129.2, 125.4, 122.8, 119.4, 115.7 (q, J = 289 Hz),114.1, 100.9, 79.9; MS *m/e* (relative intensity) 321 (M^+, 100), 252 (30), 224 (84). Anal. Calcd. for $C_{18}H_{18}F_3ON$: C, 67.28; H, 5.65; N, 4.36. Found: C, 66.83; H, 5.25; N, 4.12.

From 2-Ethynylaniline (Procedure C). 2-(2-Thienyl)ethynyltrifluoroacetanilide (19e). To a solution of 2-ethynylaniline (0.356 g, 3.03 mmol) in DMF (1.5 mL) were added 2-thienyl iodide (0.34 mL, 3.07 mmol), diethylamine (6 mL), $Pd(PPh_3)_4$ (0.035 g, 0.03 mmol), and CuI (0.012 g, 0.06 mmol). The reaction mixture was stirred at room temperature for 12 h and extracted with 1 N HCl and diethyl ether. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried (Na_2SO_4) and evaporated at the rotary evaporator.

The crude coupling product was further kept under vacuum (~1 mm/Hg) for 2 h and dissolved in anhydrous dichloromethane (20 mL). 2,6-di-*tert*-Butyl-4-methylpyridine (0.808 g, 3.94 mmol) and, after cooling in an ice bath, trifluoroacetic anhydride (0.55 mL, 3.94 mmol) were added. The reaction mixture was stirred at room temperature for 7 h and extracted with saturated Na_2CO_3 solution and dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with *n*-hexane to give 0.77 g (86% yield) of **19e**: mp 110-2 °C; IR 3280, 2170, 1700 cm^{-1}; ^1H NMR δ 8.77 (bs, 1 H), 8.36 (d, J = 7.9 Hz, 1 H), 7.56-7.51 (m, 1 H), 7.46-7.32 (m, 3 H), 7.21 (dt, J = 7.7 Hz, J = 1.2 Hz, 1 H), 7.09-7.03 (m, 1 H); ^{13}C NMR δ 154.4 (q, J = 37 Hz),135.9, 132.9, 131.5, 130.0, 128.7, 127.5, 125.6, 121.4, 119.8, 115.7 (q, J = 289 Hz),113.3, 91.2, 86.6; MS *m/e* (relative intensity) 297 (M^+, 6), 295 (M^+, 100), 226 (23), 198 (97). Anal. Calcd. for $C_{14}H_8F_3ONS$: C, 56.95; H, 2.73; N, 4.74. Found: C, 57.22; H, 3.02; N, 4.39.

2-(hex-1-ynyl)trifluoroacetanilide (19a) (Procedure A): 81% yield; oil; IR (neat) 3330, 2200, 1720 cm^{-1}; ^1H NMR δ 8.85 (bs, 1 H), 8.34 (d, J = 8.3 Hz, 1 H), 7.45-7.34 (m, 2 H), 7.14 (dt, J = 7.6 Hz, J = 1.2 Hz, 1 H) , 2.52 (t, J = 6.8 Hz, 2 H), 1.63-1.47 (m, 4 H), 0.97 (t, J= 7.1 Hz, 3 H); ^{13}C NMR δ 154.4 (q, J = 37 Hz), 136.2, 131.6, 129.0, 125.3, 119.3, 115.7 (q, J = 289 Hz), 114.1, 99.6, 74.7, 30.6, 22.0, 19.1, 13.5; MS *m/e* (relative intensity) 269 (M^+, 97), 227 (86), 200 (55), 172 (31). Anal. Calcd. for $C_{14}H_{14}F_3ON$: C, 62.45; H, 5.24; N, 5.2. Found: C, 61.92; H, 5.59; N, 4.71.

2-(Prop-1-ynyl)trifluoacetanilide (19d) (Procedure A): [preparation of **19d** was performed using $PdCl_2(PPh_3)_2$ and under a 4 atm pressure of propyne] 87% yield; mp 74-6 °C; IR 3340, 2210, 1720 cm^{-1}; ^1N NMR δ 8.80 (bs, 1 H), 8.29 (d, J = 8.3 Hz, 1 H), 7.41-7.24 (m, 2 H), 7.10 (dt, J = 7.6 Hz, J = 1.2 Hz, 1 H), 2.13 (s, 3 H); ^{13}C NMR δ 154.5 (q, J = 37 Hz), 136.3, 131.7, 129.1, 125.4, 119.4, 115.9 (q, J = 289 Hz), 114.3, 95.1, 74.0, 4.3; MS *m/e* (relative intensity) 227 (M^+, 100), 130 (75). Anal. Calcd. for $C_{11}H_8F_3ON$: C, 58.16; H, 3.55; N, 6.17. Found: C, 58.75; H, 3.82; N, 5.89.

2-(6-Methoxy-3,4-dihydro-1-naphthyl)ethynyltrifluoroacetanilide (19f) (Procedure B): [preparation of **19f** was performed using 3 mol % of $Pd(PPh_3)_4$ and 6 mol % of CuI] 72% yield; mp 79-81 °C; IR 3360, 2200, 1720 cm^{-1}; ^1H NMR δ 8.86 (bs, 1 H), 8.38 (d, J = 8.8 Hz, 1 H), 7.59-7.38 (m, 3 H), 7.19 (dt, J = 8.2 Hz, J = 1.2 Hz, 1 H), 6.81-6.70 (m, 2 H), 6.49 (t, J = 4.9 Hz, 1 H), 3.83 (s, 3 H), 2.84 (t, J = 7.8 Hz, 2 H), 2.51-2.41 (m, 2 H); ^{13}C NMR δ 159.5, 154.5 (q, J = 37 Hz), 136.8, 135.9, 134.8, 131.9, 129.6, 125.9, 125.5, 124.9, 120.5, 119.7, 115.7 (q, J = 289 Hz), 113.9, 113.8, 111.3, 96.4, 83.5, 55.3, 27.5, 23.8; MS *m/e* (relative intensity) 371 (M^+, 100), 302 (13), 274 (61). Anal. Calcd. for $C_{21}H_{16}F_3O_2N$: C, 67.92; H, 4.34; N, 3.77. Found: C, 70.12; H, 4.41; N, 3.95.

2-(3-Methylphenyl)ethynyltrifluoroacetanilide (19g) (Procedure B): 59% yield; mp 110-111 °C; IR 3270, 1700 cm^{-1}; ^1H NMR δ 8.87 (bs, 1 H), 8.34 (d, J = 8.2 Hz, 1 H), 7.55-7.19 (m, 7 H), 2.34 (s, 3

H); ^{13}C NMR δ 154.4 (q, J = 37 Hz), 138.5, 136.1, 132.0, 131.7, 130.3, 129.8, 128.62, 128.59, 125.5, 121.6, 119.6, 115.8 (q, J = 289 Hz), 113.6, 98.4, 82.6, 21.2; MS *m/e* (relative intensity) 303 (M^+, 100), 234 (41), 206 (29). Anal. Calcd. for $C_{17}H_{12}F_3ON$: C, 67.33; H, 3.99; N, 4.62. Found: C, 66.98; H, 4.15; N, 4.49.

Preparation of 2-Ethynyltrifluoroacetanilide. To a stirred solution of 2-iodoaniline (3.0 g, 13.70 mmol) in DMF (2 mL) and Et_2NH (15 mL) were added trimethylsilylacetylene (2.84 mL, 20.54 mmol), $Pd(PPh_3)_4$ (0.079 g, 0.068 mmol), and CuI (0.026 g, 0.137 mmol). The reaction mixture was stirred overnight under nitrogen at room temperature and poured in a separatory funnel containing diethyl ether and 0.1 N HCl. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and evaporated under vacuum.

The residue was dissolved in methanol (70 mL) and potassium fluoride (2.95 g, 50.77 mmol) was added. The reaction mixture was stirred for 5 h at room temperature, methanol was partially evaporated to around 1/4 of its original volume and the resultant mixture was extracted with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and evaporated on the rotary evaporator.

The residue was connected to a vacuum line, kept at 1 mm/Hg for 2 h, and dissolved in anhydrous CH_2Cl_2 (20 mL). Then, 2,6-di-*tert*- butyl-4-methylpyridine (3.09 g, 15.05 mmol) was added and the flask was cooled in an ice bath.Trifluoroacetic anhydride (2.2 mL, 15.05 mmol) was added, the reaction mixture was stirred under nitrogen for 3 h at room temperature, and extracted with CH_2Cl_2 and saturated Na_2CO_3. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel eluting with a *n*-hexane/EtOAc 95/5 (v/v) mixture to give 2.08 g (71% yield) of 2-ethynyltrifluoroacetanilide: mp 35-7 °C; IR 3250, 2080, 1710 cm^{-1}; ^1H NMR δ 8.74 (bs, 1 H), 8.34 (d, J = 8.3 Hz, 1 H), 7.54-7.37 (m, 2 H), 7.18 (dt, J = 7.6 Hz, J = 1.2 Hz, 1 H), 3.61 (s, 1 H); ^{13}C NMR δ 154.6 (q, J = 37 Hz), 136.9, 132.4, 130.5, 125.5, 119.7, 115.4 (q, J = 289 Hz), 112.2, 85.8, 77.9; MS *m/e* (relative intensity): 213 (M^+, 97), 144 (20), 116 (100). Anal. Calcd. for $C_{10}H_6F_3ON$: C, 56.35; H, 2.84; N, 6.57. Found: C, 56.64; H, 2.95; N, 6.39.

Preparation of N-methyl-2-Phenylethynyltrifluoroacetanilide (35). To a stirred solution of 2-phenylethynyltrifluoroacetanilide **19c** (0.603 g, 2.08 mmol) in CH_2Cl_2 (6 mL) were added *n*-Bu_4NHSO_4 (0.708 g, 2.08 mmol), 1 N NaOH (4.1 mL), and methyl iodide (0.234 mL, 3.75 mmol). The reaction mixture was stirred at 50 °C (bath temperature) for 1.5 h. The organic layer was separated, diluted with CH_2Cl_2, washed with 1 N HCl, saturated $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated at the rotary evaporator. The residue was purified by flash chromatography on silica gel eluting with a *n*-hexane/EtOAc 95/5 (v/v) mixture to give 0.498 g (79% yield) of **35**: mp 49-51; IR 2200, 1700 cm^{-1}; ^1H NMR δ 7.63-7.24 (m, 9 H), 3.40 (s, 3 H); ^{13}C NMR δ 157.3 (q, J = 36 Hz), 113.4 (q, J = 288 Hz), 95.3, 84.3, 38.4; MS *m/e* (relative intensity) 303 (M^+, 100), 234 (89), 206 (88). Anal. Calcd. for $C_{17}H_{12}F_3ON$: C, 67.33; H, 3.99; N, 4.62. Found: C, 67.71; H, 4.12; N, 4.47.

Typical Procedure for the Synthesis of 2-Substituted-3-acylindoles (21). 2-(cyclooct-1-enyl)-3-(4-methoxybenzoyl)indole (21d). To a solution of 2-(cyclooct-1-enyl)trifluoroacetanilide **19b** (0.180 g, 0.56 mmol) in acetonitrile (6 mL) were added 4-methoxyphenyl iodide (0.157 g, 0.67 mmol), K_2CO_3 (0.387 g, 2.80 mmol), and $Pd(PPh_3)_4$ (0.032 g, 0.028 mmol). The flask was purged with carbon monoxide for few seconds and connected to a balloon of carbon monoxide. The reaction mixture was stirred at 45 °C overnight and poured in a separatory funnel containing 0.1 N HCl and ethyl acetate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with a 80/20 *n*-hexane/EtOAc mixture to give 0.155 g (77% yield) of **21d**: mp 72-6 °C; IR 3250, 1590 cm^{-1}; ^1H NMR δ 8.45 (bs, 1 H), 7.82 (AA' part of an AA'BB' system, J = 8.9 Hz, 2 H), 7.71-7.64 (m, 1 H),

7.40-7.34 (m, 2 H), 7.25-7.08 (m, 2 H), 6.88 (BB' part of an AA'BB' system, J = 8.9 Hz, 2 H), 6.06 (t, J = 8.2 Hz, 1 H), 3.87 (s, 3 H), 2.38-2.27 (m, 2 H), 2.21-2.08 (m, 2 H), 1.46 (bs, 8 H); ^{13}C NMR δ 192.5, 162.7, 145.9, 134.8, 134.4, 133.6, 133.2, 131.9, 128.5, 122.6, 121.4, 120.9, 113.2, 112.6, 111.0, 55.4; MS *m/e* (relative intensity) 359 (M^+, 51), 135 (60). Anal. Calcd. for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.77; H, 7.12; N, 4.56.

2-*n*-Butyl-3-(4-methoxybenzoyl)indole (21a): mp 123-125 °C; IR (CCl_4) 3480, 1610 cm^{-1}; ^{1}H NMR δ 9.36 (bs, 1 H), 7.80 (AA' part of an AA'BB' system, J = 8.7 Hz, 2 H), 7.36-7.30 (m, 2 H), 7.19-7.00 (m, 2 H), 6.94 (BB' part of an AA'BB' system, J = 8.7 Hz, 2 H), 3.88 (s, 3 H), 2.92 (t, J =7.5 Hz, 2H), 1.88-1.57 (m, 2 H), 1.32-1.21 (m, 2 H), 0.81 (t, J =7.3 Hz, 3 H); ^{13}C NMR δ 192.4, 162.7, 147.6, 134.8, 133.6, 131.5, 127.6, 122.1, 121.1, 120.8, 113.5, 113.4, 110.9, 55.4, 31.7, 27.5, 22.5, 13.8; MS *m/e* (relative intensity) 307 (M^+, 100), 278 (92), 264 (71), 135(79). Anal. Calcd. for $C_{20}H_{21}O_2N$: C, 78.15; H, 6.89; N, 4.56. Found: C, 79.34; H, 7.12; N, 4.86.

2-*n*-Butyl-3-(4-acetamidobenzoyl)indole (21b): mp 125-127 °C; IR 3280, 1690, 1610 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.85 (bs, 1 H), 10.26 (bs, 1 H), 7.74 (AA' part of an AA'BB' system, J = 8.7 Hz, 2 H), 7.64 (BB' part of an AA'BB' system, J = 8.7 Hz, 2 H), 7.41 (d, J = 8 Hz, 1 H), 7.27, (d, J 7.8 Hz, 1 H), 7.15-6.96 (m, 2 H), 2.86 (t, J = 7.7 Hz, 2 H), 2.12 (s, 3 H), 1.73-1.58 (m, 2 H), 1.35-1.18 (m, 2 H), 0.84 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 190.8, 168.7, 147.7, 142.2, 135.6, 135.0, 129.6, 127.2, 121.5, 120.5, 120.0, 118.0, 112.3, 111.3, 31.3, 26.8, 24.1, 21.9, 13.5; MS *m/e* (relative intensity) 334 (M^+, 100), 291 (68), 162 (95). Anal. Calcd. for $C_{21}H_{22}O_2N_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.90; H, 6.93; N, 8.05.

2-*n*-Butyl-3-(4-chlorobenzoyl)indole (21c): mp 160-1 °C; IR 3240, 1610 cm^{-1}; ^{1}H NMR δ 9.12 (bs, 1 H), 7.73 (AA' part of an AA'BB' system, J = 8.4 Hz, 2 H), 7.43 (BB' part of an AA'BB' system, J = 8.4 Hz, 2 H), 7.33-7.02 (m, 4 H), 2.95 (t, J = 7.7 Hz, 2 H), 1.74-1.59 (m, 2 H), 1.40-1.22 (m, 2 H), 0.85 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 191.9, 148.6, 139.5, 137.6, 134.7, 130.5, 128.6, 127.4, 122.5, 121.6, 120.8, 113.1, 110.9, 31.6, 27.7, 22.5, 13.7; MS *m/e* (relative intensity) 313 (M^+, 20), 311 (M^+, 60), 141 (35), 139 (100). Anal. Calcd. for $C_{19}H_{18}ClON$: C, 73.19; H, 5.82; N, 4.49. Found: C, 73.94; H, 6.04; N, 4.25.

2-Phenyl-3-(3-methylbenzoyl)indole (21e): mp 178-180 °C; IR (CCl_4) 3420, 1620 cm^{-1}; ^{1}H NMR δ 9.33 (bs, 1 H), 7.94–7.89 (m, 1 H), 7.38–7.02 (m, 12 H), 2.13 (s, 3 H); ^{13}C NMR δ 193.8, 144.1, 139.5, 137.3, 135.6, 132.3, 131.8, 130.4, 129.2, 128.6, 128.1, 127.7, 126.9, 123.4, 122.1, 121.6, 113.6, 111.2, 21.0; MS *m/e* (relative intensity) 311 (M^+, 51), 220 (100). Anal. Calcd. for $C_{22}H_{17}ON$: C, 84.86; H, 5.5; N, 4.5. Found: C, 84.12; H, 5.64; N, 4.25.

2-Phenyl-3-(4-methoxybenzoyl)indole (21f): mp 153-5 °C; IR (KBr) 3200, 1590 cm^{-1}; ^{1}H NMR δ 8.70 (bs, 1 H), 7.86-7.80 (m, 1 H), 7.69 (AA' part of an AA'BB' system, J = 8.9 Hz, 2 H), 7.45-7.36 (m, 3 H), 7.31-7.16 (m, 6 H), 6.70 (BB' part of an AA'BB' system, J = 8.9 Hz, 2 H), 3.78 (s, 3 H); ^{13}C NMR δ 192.5, 162.6, 143.0, 135.6, 132.2, 132.1, 131.7, 129.0, 128.6, 128.5, 128.3, 123.2, 121.7, 121.3, 113.6, 113.1, 111.3, 55.3; MS m/e (relative intensity) 327 (M^+, 88), 220 (100). Anal. Calcd. for $C_{22}H_{17}O_2N$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.54; H, 5.41; N, 4.52.

2-Methyl-3-(4-methoxybenzoyl)indole (21g): mp 213-5 °C (lit[14a] mp 215-217 °C); IR ($CHCl_3$) 3480, 1610 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.90 (bs, 1 H), 7.66 (AA' part of an AA'BB' system, J = 8.7 Hz, 2 H), 7.43-7.35 (m, 2 H), 7.16-6.98 (m, 4 H), 3.84 (s, 3 H), 2.44 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 190.4, 161.8, 143.3, 134.9, 133.5, 130.7, 127.3, 121.5, 120.6, 119.9, 113.4, 112.6, 111.1, 55.3, 14.0; MS m/e (relative intensity) 265 (M^+, 76), 264? (100), 158 (43). Anal. Calcd. for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.7; N, 5.28. Found: C, 77.06; H, 5.94; N, 4.99.

2-Thienyl-3-(4-methylbenzoyl)indole (21h): mp 142-4 °C; IR ($CHCl_3$) 3450, 1610 cm^{-1}; ^{1}H NMR δ 9.48 (bs, 1 H), 7.67 (AA' part of an AA'BB' system, J = 8.0 Hz, 2 H), 7.50 (d, J = 7.5 Hz, 1 H), 7.37-7.03 (m, 7 H), 6.83-6.77 (m, 1 H), 2.34 (s, 3 H); ^{13}C NMR δ 192.9, 142.8, 137.0, 136.3, 135.4, 132.7, 129.9, 128.8, 128.7, 128.3, 127.6, 127.4, 123.4, 121.6, 121.3, 113.9, 111.2, 21.6; MS m/e (relative intensity) 319

(M^+, 5), 317 (M^+, 72), 226 (100). Anal. Calcd. for $C_{20}H_{15}ONS$: C, 75.68; H, 4.76; N, 4.41. Found: C, 75.26; H, 5.03; N, 4.35.

2-(6-Methoxy-3,4-dihydro-1-naphthyl)-3-(3-fluorobenzoyl)indole (21i): mp 167-170 °C; IR (KBr) 3220, 1590 cm^{-1}; ^1H NMR δ 9.05 (bs, 1 H), 8.20-8.16 (m, 1 H), 7.40-6.88 (m, 8 H), 6.57-6.52 (m, 2 H), 5.94 (t, J = 4.7 Hz, 1 H), 3.74 (s, 3 H), 2.40 (t, J = 8 Hz, 2 H), 2.04-1.93 (m, 2 H); ^{13}C NMR δ 192.1, 55.3, 27.5, 23.1; MS m/e (relative intensity) 397 (M^+, 100), 302 (22), 123 (78). Anal. Calcd. for $C_{26}H_{20}FO_2N$: C, 78.57; H, 5.07; N, 3.52. Found: C, 79.00; H, 5.30; N, 3.40.

2-*n*-Butyl-3-(4-carbomethoxybenzoyl)indole (21j): mp 148-150 °C; IR (KBr): 3210, 1710, 1580 cm^{-1}; ^1H NMR δ 9.75 (bs, 1 H), 8.16 (AA' part of an AA'BB' system, J = 8.1 Hz, 2 H), 7.80 (BB' part of an AA'BB' system, J = 8.1 Hz, 2 H), 7.32-7.00 (m, 4 H), 3.97 (s, 3 H), 2.93 (t, J = 8.1 Hz, 2 H), 1.73-1.58 (m, 2 H), 1.36-1.18 (m, 2 H), 0.81 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 192.6, 166.7, 149.6, 145.5, 134.9, 132.3, 129.7, 128.6, 127.4, 122.5, 121.7, 120.7, 112.9, 111.1, 52.4, 31.6, 27.8, 22.5, 13.7; MS m/e (relative intensity) 335 (M^+, 86), 306 (70), 292 (58), 163 (100). Anal. Calcd. for $C_{21}H_{21}O_3N$: C, 75.2; H, 6.31; N, 4.18. Found: C, 75.95; H, 6.54; N, 3.78.

2-*n*-Butyl-3-(cyclooct-1-enecarbonyl)indole (21k): mp 114-6 °C. IR (CCl_4) 3430, 1610 cm^1; ^1H NMR δ 8.93 (bs, 1 H), 7.77-7.72 (m, 1 H), 7.28-7.33 (m, 1 H), 7.13-7.09 (m, 2 H), 6.63 (t, J = 8.3 Hz, 1 H), 2.91 (t, J =7.7 Hz, 2 H), 2.65-2.58 (m, 2 H), 2.30-2.40 (m, 2 H), 1.77-1.23 (m, 12 H), 0.85 (t, J = 7 .3 Hz, 3 H); ^{13}C NMR δ 195.3, 145.6, 143.9, 143.3, 134.7, 127.8, 121.8, 120.9, 120.7, 113.4, 110.7, 31.7, 30.2, 28.8, 27.4, 27.3, 26.7, 26.2, 25.6, 22.5, 13.8; MS m/e (relative intensity) 309 (M^+, 57), 238 (100), 200 (47). Anal. Calcd. for $C_{21}H_{27}ON$: C, 81.51; H, 8.79; N, 4.53. Found: C, 80.65; H, 9.16; N, 4.02.

2-*n*-Butyl-3-(4-phenylcyclohex-1-enecarbonyl)indole (21l): mp 127-9 °C; IR(CCl_4):3430, 1610 cm^{-1}; ^1H NMR δ 9.27 (bs, 1 H), 7.85-7.78 (m, 1 H), 7.37-7.10 (m, 8 H), 6.63 (bs, 1 H), 2.98 (t, J = 7.8 Hz, 2 H), 2.90-2.05 (m, 6 H), 1.96-1.76 (m, 1 H), 1.74-1.58 (m, 2 H), 1.42-1.24 (m, 2 H), 0.88 (t, J =7.0 Hz, 3 H); ^{13}C NMR δ 194.1, 146.1, 145.1, 139.7, 137.1, 134.0, 127.5, 126.7, 125.8, 125.3, 121.0, 120.1, 119.5, 112.1, 110.1, 38.6, 32.9, 30.8, 28.6, 26.6, 24.1, 21.6, 12.8; MS m/e (relative intensity) 357 (M^+, 100), 315(55), 314(65), 200(37). Anal. Calcd. for $C_{25}H_{27}ON$: C, 83.99; H, 7.61; N, 3.92. Found: C, 84.52; H, 7.89; N, 3.71.

2-Phenyl-3-(3,3,5,5-tetramethylcyclohex-1-enecarbonyl)indole (21m): mp 203-5 °C; IR (CCl_4) 3420, 1610 cm^{-1}; ^1H NMR δ 8.97 (bs, 1 H), 8.00-7.96 (m, 1 H), 7.42-7.17 (m, 8 H), 6.05, (s, 1 H), 2.16 (s, 2 H), 1.15 (s, 2 H), 0.89 (s, 6 H), 0.57 (s, 6 H); ^{13}C NMR δ 196.1, 150.6, 141.9, 156.1, 135.9, 132.7, 129.2, 128.7, 128.6, 128.4, 123.1, 121.5, 121.0, 113.4, 111.3, 49.2, 37.3, 33.2; MS m/e (relative intensity) 357 (M^+, 35), 220 (100), 165 (28).Anal. Calcd. for $C_{25}H_{27}ON$: C, 83.99; H, 7.61; N, 3.92. Found: C, 84.32; H, 7.97; N, 3.59.

2-Phenyl-3-(17-oxo-androsta-3,5-diene-3-carbonyl)indole (21p): mp 232-233 °C; IR (KBr) 3300, 1750, 1610 cm^{-1}; ^1H NMR δ 9.77 (bs, 1 H), 7.93-7.88 (m, 1 H), 7.40-7.33 (m, 1 H), 7.20-7.00 (m, 6 H), 6.41 (s, 1 H), 5.34 (bs, 1 H), 2.24 (s, 3 H), 0.84 (s, 3 H), 0.60 (s, 3 H); ^{13}C NMR δ 221.2, 195.2, 142.5, 141.7, 140.8, 138.0, 135.8, 135.7, 132.5, 129.9, 129.0, 128.5, 128.4, 125.7, 122.9, 121.4, 121.4, 120.8, 113.6, 111.3; MS m/e 503 (M^+). Anal. Calcd. for $C_{35}H_{37}O_2N$: C, 83.46; H, 7.4; N, 2.78. Found: C, 83.95; H, 7.99; N, 2.40.

2-Phenyl-3-(4-*tert*-butylcyclohex-1-enecarbonyl)indole (21q): mp 239-240 °C; IR ($CHCl_3$) 3410, 1590 cm^{-1}; ^1H NMR δ 8.60 (bs, 1 H), 8.04-7.99 (m, 1 H), 7.42-7.22 (m, 8 H), 6.31-6.24 (m, 1 H), 0.76 (s, 9 H); ^{13}C NMR δ 195.0, 142.3, 142.3, 142.2, 139.4, 135.5, 132.9, 129.1, 128.6, 128.5, 123.4, 121.9, 121.5, 114.3, 110.9, 43.2, 32.0, 27.5, 27.0, 25.6, 23.3; MS m/e (relative intensity) 357 (M^+, 60), 220 (100), 165 (41). Anal. Calcd. for $C_{25}H_{27}ON$: C, 83.99; H, 7.61; N, 3.92. Found: C, 84.18; H, 7.88; N, 3.10.

2-(*n*-Butyl)-3-(phenylacetyl)indole (21r): mp 108-9 °C; IR 3200, 1610 cm^{-1}; ^1H NMR δ 8.99 (bs, 1 H), 8.05-8.01 (m, 1 H), 7.36-7.16 (m, 8 H), 4.37 (s, 1 H), 3.09 (t, J = 7.8 Hz, 2 H), 1.73-1.57 (m, 2 H) 1.43-1.25 (m, 2 H), 0.87 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 195.4, 149.4, 135.3, 134.7, 129.7, 128.4, 126.6,

126.5, 122.3, 122.0, 120.8, 113.4, 111.3, 49.3, 31.0, 28.7, 22.7, 13.8; MS m/e (relative intensity) 291 (M^+, 5), 200 (100). Anal. Calcd. for $C_{20}H_{21}ON$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.10; H, 7.35; N, 4.54.

Palladium-Catalysed Carbonylative Cyclization of 2-(hex-1-ynyl)trifluoroacetanilide (19a) with 4-Methoxyphenyl Iodide in the Presence of Methanol. To a solution of **19a** (1.0 g, 3.71 mmol) in MeCN (15 mL) were added 4-methoxyphenyl iodide (1.043 g, 4.46 mmol), K_2CO_3 (2.566 g, 18.57 mmol), $Pd(PPh_3)_4$ (0.214 g, 0.18 mmol), and methanol (0.053 mL, 1.3 mmol). The reaction flask was purged with a small flow of carbon monoxide for few seconds and connected to a balloon filled with carbon monoxide. The reaction mixture was stirred at 45 °C overnight and worked-up as usual. The residue was purified by flash chromatography on silica gel eluting with *n*-hexane/EtOAc mixtures [gradient from 95/5 (v/V) to 75/25 (v/v)] to give 0.340 g (34%) of recovered **19a**, 0.118 g (16%) of methyl 4-iodobenzoate, 0.524 g (46%) of 2-*n*-butyl-3-(4-methoxybenzoyl)indole **21a**, and 0.017 g (2%) of 2-*n*-butyl-3-methoxycarbonyl indole **36**: mp 149-151 °C (lit.[21] mp 150-1 °C).

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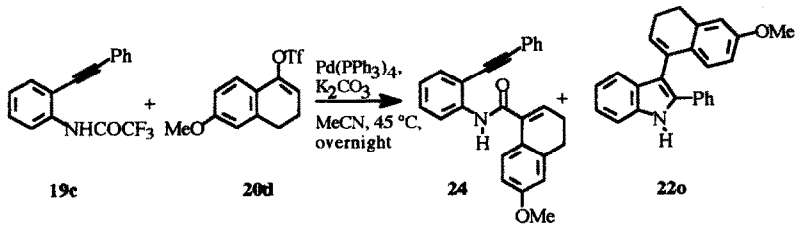
20. For example, **19c**, on reaction with 6-methoxy-3,4-dihydro-1-naphthyl triflate **20d**, afforded the amide **24** in 20% yield and the non-carbonylated 2,3-disubstituted-indole **22o** in 24% yield along with other unidentified products.



19c **20d** **24** **22o**

P_{CO} = 1 atm	20%	24%
P_{CO} = 7 atm	42%	traces
P_{CO} = 7 atm (*n*-Bu_4NCl)	22%	traces

Formation of the amide **24** does not seem to involve the initial hydrolysis of **19c** followed by the nucleophilic attack of the resultant 2-phenylethynylaniline on the σ-acylpalladium complex as it might be supposed. At least, experimental data suggest that this sequence does not represent the main reaction pathway. Indeed, **19c** was found to undergo the hydrolytic cleavage of the amide bond only to a very limited extent. Treating it under usual conditions, in the absence of **20d**, led to its recovery in 85% yield and 2-phenylethynylaniline was detected only in trace amounts. Most probably, the formation of the amide **24** can be accounted for by the intermolecular nucleophilic attack of the nitrogen anion on the approaching σ-acylpalladium complex. Accordingly, trifluoroacetanilide was found to react with 6-methoxy-1-naphthyl triflate under a balloon of carbon monoxide producing the corresponding amide in 28 % yield. However, generation of the amide derivative through intramolecular nucleophilic attack of the nitrogen anion on the σ-acylpalladium moiety of a π-alkynyl-σ-acylpalladium complex **27** (see Scheme 8) cannot be excluded.

21. In the absence of carbon monoxide, 2-*n*-butyl-3-benzyl indole was isolated in 13% yield at room temperature and in 47% yield at 80 °C. The N-benzyl derivative of the starting 2-alkynyltrifluoroacetanilide was isolated in 76 and 50% yield, respectively..
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26. **20g**: oil; IR (neat) 1420, 1210 cm^{-1}; ^1H NMR (200 MHz) ($CDCl_3$) δ 5.73 (bs, 1 H), 2.40-2.10 (m, 3 H), 2.05-1.85 (m, 2 H), 1.40-1.25 (m, 2 H), 0.89 (s, 9 H); ^{13}C NMR (50.3 MHz) ($CDCl_3$) δ 149.3, 121.8, 118.6 (q, J = 320 Hz), 118.5, 43.0, 32.1, 28.6, 27.3, 25.4, 24.2.
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