Preparation of Indoles from *o*-Alkynyltrifluoroacetanilides Through the Aminopalladation-Reductive Elimination Process

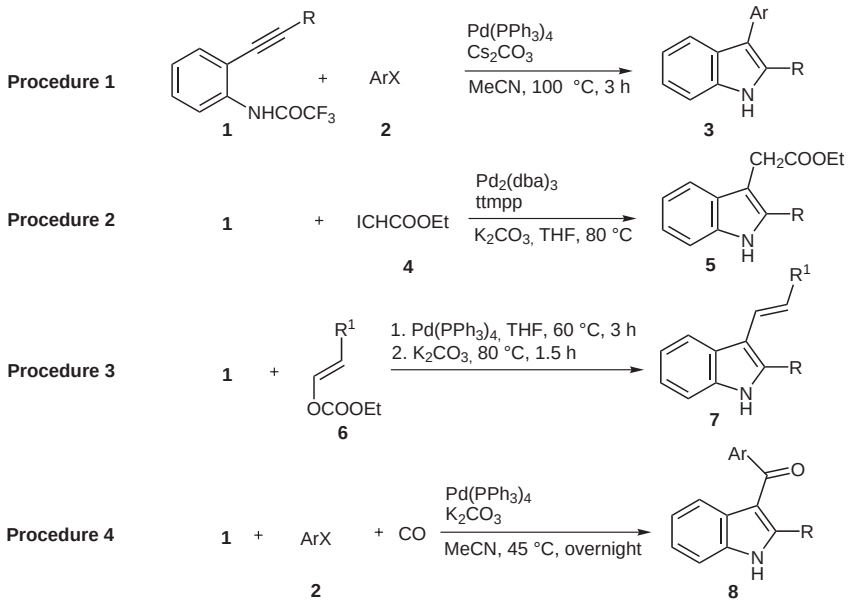
Sandro Cacchi,* Giancarlo Fabrizi, Luca M. Parisi

Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi 'La Sapienza', P. le A. Moro 5, 00185 Roma, Italy
Fax +39(6)49912780; E-mail: sandro.cacchi@uniroma1.it

Received 22 December 2003; revised 14 January 2004

Abstract: The functionalized pyrrole nucleus contained in the indole system has been assembled via the palladium-catalyzed reaction of *o*-alkynyltrifluoroacetanilides with organic halides/triflates or allyl carbonates. In the presence of carbon monoxide, a three-component reaction can take place and indole derivatives incorporating a molecule of carbon monoxide have been obtained.

Key words: indoles, alkynes, cyclization, palladium, catalysis



Scheme 1

Introduction

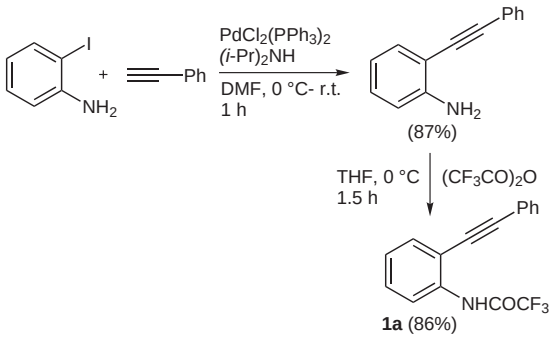
The substituted indole nucleus is a structural component of a vast number of biologically active natural and unnatural compounds. One of the strategies most commonly used in the preparation of indole derivatives is based on the construction of the pyrrole ring contained in the indole system. A great deal of studies has been directed towards this issue, including those involving palladium-catalyzed reactions.[1] During our ongoing investigation on the utilization of palladium catalysis in the synthesis of heterocycles, we have shown that *o*-alkynytrifluoroacetanilides are very useful building blocks for the assembly of the pyrrole nucleus of indoles.[2] The use of the trifluoroacetamido group was found to be particularly suited for favoring cyclization processes involving η^2-alkyne-organopalladium intermediates.[3] In addition, it allows for the formation of free NH pyrrole nuclei (the amide bond is broken during the reaction or/and the workup), avoiding troublesome and time-consuming deprotecting steps. Herein we show that the broad tolerance of a variety of aryl, heteroaryl, vinyl halides or triflates, alkyl halides, and allyl carbonates as well as of a variety of substituents in the starting alkyne makes this process a versatile and valuable tool for the preparation of substituted indoles. In the presence of carbon monoxide, a three-component reaction allows the synthesis of functionalized indole products incorporating a molecule of carbon monoxide (Scheme 1).

Scope and Limitations

The preparation of the starting *o*-alkynyltrifluoroacetanilides **1** is detailed in Scheme 2 for *o*-(phenylethynyl)tri-

SYNTHESIS 2004, No. 11, pp 1889–1894
Advanced online publication: 03.03.2004
DOI: 10.1055/s-2004-815993; Art ID: Z18403SS

fluoroacetanilide **1a** (R = Ph). The Sonogashira coupling[4] of phenylacetylene with *o*-iodoaniline affords *o*-(phenylethynyl)aniline which, upon treatment with trifluoroacetic anhydride, gives **1a** in an approximately 75% overall yield. Alternatively, compounds **1** can be prepared through the palladium-catalyzed reaction of readily available *o*-ethynyltrifluoroacetanilide[5] with aryl and vinyl halides or triflates.



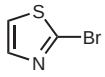
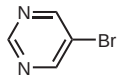
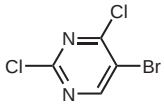
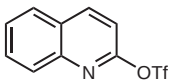
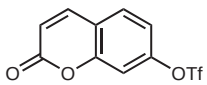
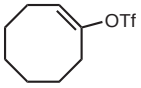
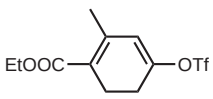
Scheme 2

The reaction of **1** with aryl, heteroaryl, and vinyl halides or triflates **2** affords the corresponding indole products **3**[3,6] (Procedure 1, Scheme 1). As shown in Table 1, the reaction tolerates, in the $C_{sp}2$ donor, various functional groups amenable of further functionalization. Aryl halides and triflates containing aldehyde, ketone, ester, nitro, nitrile functionality all afforded the desired indole products usually in excellent yields. Substituents close to the oxidative addition site do not hamper the reaction (entries 3 and 18). As for the alkyne component (Table 2), indole derivatives have been obtained in moderate to high yields with alkynes containing alkyl and vinyl substituents as well as aryl substituents with electron-withdrawing and electron-donating groups. The same reaction conditions, however, do not provide satisfactory results when *o*-ethynyltrifluoroacetanilide is used as the starting alkyne to prepare 2-unsubstituted 3-arylindoles. In this case, slightly different reaction conditions have been developed.[7]

Extension of this methodology to ethyl iodoacetate produces the indolylcarboxylate esters **5** in good yields[8] (Procedure 2, Scheme 1). Some of our preparative results are listed in Table 3. The nature of the group R joined to one of the acetylenic carbons was found to influence the reaction outcome and formation of variable amounts of *N*-alkyl derivatives and 2-ethoxycarbonyl-3-alkylindoles[9] as by-products can be observed. However, satisfactory results have been usually obtained under the conditions shown and the reaction appears to tolerate the presence of electron-donating and electron-withdrawing substituents in the alkyne component. The procedure can be applied to the synthesis of 2-substituted 3-benzylindoles.[9]

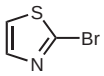
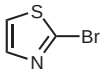
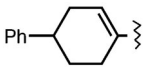
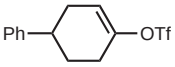
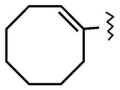
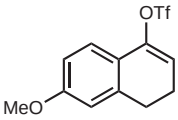
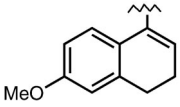
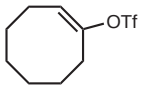
The methodology was further extended to allylic carbonates providing a straightforward approach to 2-substituted 3-allylindoles **7**.[10] The one-pot reaction (Procedure 3, Scheme 1) gives good results with a variety of allylic car

Table 1 Examples for the Synthesis of 3-Substituted 2-Phenylindoles **3** from **1a** and Aryl, Heteroaryl, and Vinyl Halides or Triflates

Entry	Aryl, Heteroaryl, Vinyl Halide or Triflate **2**	Yield (%)[a] of Indole **3**
1	*p*-MeC_6H_4Br	98
2	*m*-MeC_6H_4Br	98
3	*o*-MeC_6H_4Br	96
4	3,5-$Me_2C_6H_3Br$	98
5	*p*-$MeOC_6H_4Br$	88
6	*m*-$MeOC_6H_4Br$	86
7	*m*-FC_6H_4Br	98
8	*p*-ClC_6H_4I	80[b]
9	*m*-$CF_3C_6H_4Br$	98
10	*m*-CNC_6H_4Br	99
11	*p*-CNC_6H_4Br	90
12	*m*-$CHOC_6H_4Br$	84
13	*p*-$CHOC_6H_4Br$	94
14	*p*-$MeCOC_6H_4Br$	98
15	*p*-$NO_2C_6H_4Br$	97
16		70
17		85
18		70
19	*p*-$MeOC_6H_4OTf$	98
20	3,4,5-$(MeO)_3C_6H_2OTf$	98
21	*p*-$PhCOC_6H_4OTf$	99
22	*p*-$NO_2C_6H_4OTf$	94
23		91
24		80
25		74[c]
26		90[c]

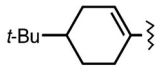
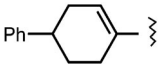
[a] Isolated yield after chromatographic purification.
[b] At 80 °C, in the presence of K_2CO_3.
[c] At room temperature, in the presence of K_2CO_3.

Table 2 Examples for the Synthesis of 2,3-Disubstituted Indoles from *o*-Alkynyltrifluoroacetanilides **1** and Aryl, Heteroaryl, and Vinyl Halides or Triflates

1 R	Aryl, Heteroaryl, Vinyl Halide or Triflate **2**	Yield (%)[a] of Indole **3**
p-$MeOC_6H_4$	*p*-*t*-BuC_6H_4Br	87
p-$MeCOC_6H_4$		74
p-$NO_2C_6H_4$		40
n-C_5H_{11}	*m*-CNC_6H_4Br	88
	*p*-$MeO_2CC_6H_4I$	68[b]
n-C_4H_9		81[c]
		89[c]
		70[c]

[a] Isolated yield after chromatographic purification.
[b] At 80 °C, in the presence of K_2CO_3.
[c] At room temperature, in the presence of K_2CO_3.

Table 3 Examples for the Synthesis of Indolylcarboxylate Esters **5** from *o*-Alkynyltrifluoroacetanilides **1** and Ethyl Iodoacetate

1 R	Yield (%)[a] of **5**	**1** R	Yield (%)[a] of **5**
m-MeC_6H_4	70	*n*-Bu	44
Ph	73		78
p-$MeCOC_6H_4$	64		41
p-$MeO_2CC_6H_4$	61		60

[a] Isolated yield after chromatographic purification.

bonates and *o*-alkynyltrifluoroacetanilides (Table 4). The presence of a substituent on the central carbon atom of the allylic system seems to be tolerated (entry 2) whereas substitution at both termini (entry 5) or sterically encumbered substituents at one end of the alkyne moiety (entry 8) hamper the cyclization reaction. Both electron-donating and electron-withdrawing substituents are tolerated on the alkyne fragment. As to the regiochemistry of the new carbon–carbon bond, the most challenging situation is posed when steric differences between the two allylic termini are small. In these cases, remarkable regioselectivity is observed in the presence of tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp) and the indole unit is located preferentially, if not exclusively, on the less substituted terminus of the allylic system (entry 10). In some cases, the process is accompanied by some loss of olefin geometry.

Table 4 Examples for the Synthesis of 2-Substituted 3-Allylindoles **7** from *o*-Alkynyltrifluoroacetanilides **1** and Allyl Carbonates **6** via a One-Pot Process

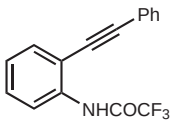
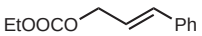
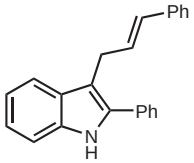
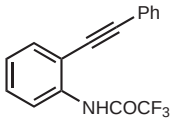
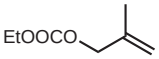
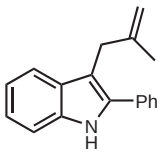
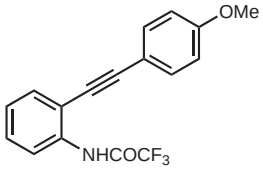
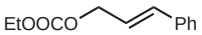
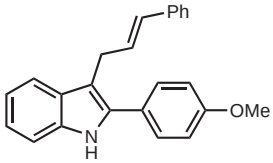
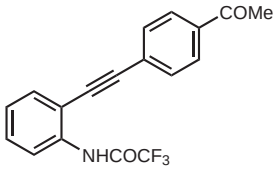
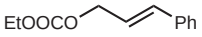
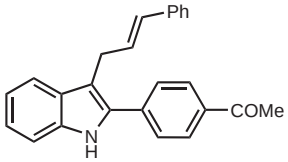
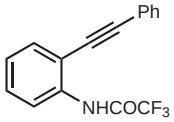
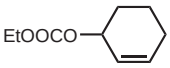
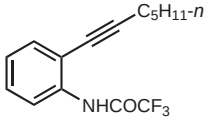
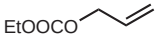
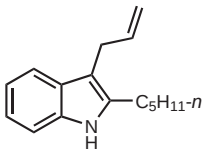
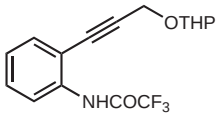
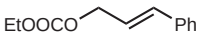
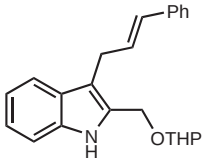
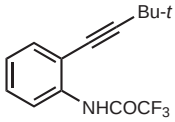
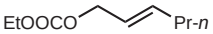
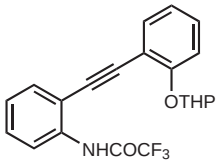
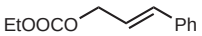
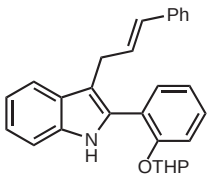
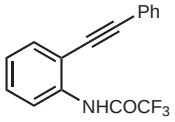
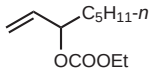
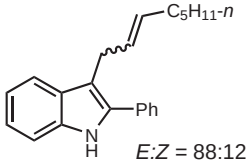
Entry	*o*-Alkynyltrifluoroacetanilide **1**	Allyl Ester **6**	3-Allylindole **7**	Yield (%)[a]
1				91
2				74
3				87

Table 4 Examples for the Synthesis of 2-Substituted 3-Allylindoles **7** from *o*-Alkynyltrifluoroacetanilides **1** and Allyl Carbonates **6** via a One-Pot Process (continued)

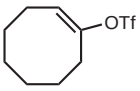
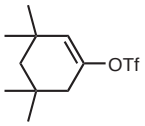
Entry	*o*-Alkynyltrifluoroacetanilide **1**	Allyl Ester **6**	3-Allylindole **7**	Yield (%)[a]
4				91
5			-[b]	
6				75
7				77
8			-[b]	
9				64
10			 *E*:*Z* = 88:12	78[c]

[a] Isolated yield after chromatographic purification.
[b] Carried out as a stepwise process [N-allylation step: $Pd_2(dba)_3$, dppb, THF, 60 °C; cyclization step: $Pd(PPh_3)_4$, K_2CO_3, MeCN, 90 °C]. No indole product was observed when the *N*-allyl intermediate was subjected to cyclization conditions.
[c] Carried out under the following reaction conditions: $Pd_2(dba)_3$, ttmpp, THF, 60 °C.

A three component procedure has been also developed in which *o*-alkynyltrifluoroacetanilides, aryl and vinyl halides or triflates, and carbon monoxide afford indole derivatives **8** incorporating a molecule of carbon monoxide[11] (Scheme 1, Procedure 4). The use of $Pd(PPh_3)_4$, in acetonitrile, under a balloon of carbon monoxide, can give satisfactory results in many cases (Table 5). With aryl halides containing electron-withdrawing groups, anhydrous acetonitrile and higher pressure of carbon monoxide are needed. The utilization of $Pd(dba)_2$/P(*o*-tol)$_3$ in acetonitrile, under a balloon of carbon monoxide, can in these cases provide an alternative, simpler procedure but its effectiveness is to be evaluated each time.

The utility of this approach to the preparation of indole products has been further demonstrated in target oriented syntheses such as the preparation of pravadoline[11] (an indole derivative designed as a nonacidic analogue of non-steroidal anti-inflammatory drugs), of rebeccamycin-related indolo[2,3-*a*]carbazole,[12] and indole inhibitors of tubulin polymerization.[13] The procedure has also been extended to a solid phase synthesis of indoles incorporating three independently variable groups.[14]

Table 5 Examples for the Synthesis of 2-Substituted 3-Acylindoles **8**

Entry	**1** R	**2**	Yield (%)[a] of Indole **8**
1	Ph	*m*-MeC_6H_4I	57
2	Ph	*p*-$MeOC_6H_4I$	60
3	*n*-Bu	*p*-$MeOC_6H_4I$	83
4	*n*-Bu	*p*-$MeCONHC_6H_4I$	72
5		*p*-MeC_6H_4I	73
6	*n*-Bu		60
7	Ph		68

[a] Isolated yield after chromatographic purification.

In summary, the aminopalladation-reductive elimination process based on the use of *o*-alkynyltrifluoroacetanilides as the starting alkynes has proved to be a powerful, very versatile tool for the preparation of a wide range of indole derivatives.

Herein, we describe four typical synthetic procedures demonstrating the scope of the aminopalladation-reductive elimination protocol. In Procedure 1 we describe the preparation of 2-phenyl-3-(pyridin-2-yl)indole starting from *o*-(phenylethynyl)trifluoroacetanilide (**1a**) and commercially available 2-bromopyridine in 88% yield. Procedures 2 and 3 show the reactions of **1a** with commercially available ethyl iodoacetate and cinnamyl ethyl carbonate to give, respectively, 2-phenyl-3-(ethoxycarbonylmethyl)indole (73% yield) and 2-phenyl-3-cinnamylindole (93% yield). In the last procedure (Procedure 4), a three component reaction is described in which **1a**, the commercially available *p*-iodoanisole, and carbon monoxide give 2-phenyl-3-(*p*-methoxybenzoyl)indole in 60% yield.

o-Phenylethynylaniline

A 100 mL three-necked round-bottom flask, equipped with a magnetic stirring bar and a 10 mL dropping funnel, was charged with *o*-iodoaniline (10.0 g, 45.66 mmol) in DMF (7 mL) and *i*-Pr_2NH (7 mL) under argon. $Pd(PPh_3)_2Cl_2$ (0.32 g, 0.46 mmol) and CuI (0.174 g, 0.91 mmol) were added and the mixture was stirred until the solubilization of CuI. The reaction mixture was cooled at 0 °C and phenylacetylene (5.5 mL, 50.23 mmol) was added dropwise in 0.5 h. Then, the reaction mixture was allowed to warm to r.t., and stirred for 1 h until the disappearance of *o*-iodoaniline (monitored by TLC). The mixture was poured into EtOAc (300 mL) and washed with aq sat. NH_4Cl (25 mL). The organic layer was separated and washed with H_2O (2 × 20 mL), dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 90:10, Macherey-Nagel silica gel 60, 0.025–0.040 mm, 200 g) to yield *o*-phenylethynylaniline as a yellow powder; yield: 7.66 g (87%); mp 89–91 °C.

IR (KBr): 3460 (s), 3366 (s), 3064 (w), 3029 (w), 2205 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.55 (m, 2 H), 7.43–7.37 (m, 4 H), 7.21–7.15 (m, 1 H), 6.79–6.75 (m, 2 H), 4.29 (br s, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 148.1, 132.6, 131.9, 130.2, 128.8, 128.6, 123.7, 118.5, 114.8, 108.4, 95.1, 86.3.

MS (EI, 70 eV): *m*/*z* (%) = 193 (M^+, 100), 165 (48).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.92; H, 5.72; N, 7.24.

o-(Phenylethynyl)trifluoroacetanilide (1a)

A 250 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with *o*-phenylethynylaniline (7.66 g, 39.69 mmol) in THF (70 mL) and cooled at 0 °C. Trifluoroacetic anhydride (11.2 mL, 79.38 mmol) was added dropwise with stirring in 0.5 h. Then, the reaction mixture was stirred at 0 °C until the disappearance of *o*-phenylethynylaniline (1.5 h, monitored by TLC). The mixture was poured into EtOAc (300 mL) and with aq sat. $NaHCO_3$ (3 × 15 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated under vacuum. The residue was connected to a vacuum line (1 mm/Hg for 2 h) to yield **1a** as a grey powder (9.90 g, 86%), which was used without further purification; mp 94–96 °C.

IR (KBr): 3344 (br), 3058 (w), 2217 (w), 1711 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.92 (br s, 1 H), 8.40 (d, *J* = 8.3 Hz, 1 H), 7.61–7.54 (m, 3 H), 7.45–7.40 (m, 4 H), 7.25 (dt, J_1 = 7.6 Hz, J_2 = 1.1 Hz, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 154.8 (q, *J* = 37.4 Hz), 136.5, 132.1, 131.9, 130.3, 1 29.7, 129.1, 126.2, 122.1, 120.0, 116.2 (q, *J* = 289.0 Hz), 113.9, 98.5, 83.3.

^{19}F NMR {H} (376.5 MHz, $CDCl_3$): δ = –75.78

MS (EI, 70 eV): *m*/*z* (%) = 289 (M^+, 56), 220 (56), 165 (100).

Anal. Calcd for $C_{16}H_{10}F_3NO$: C, 66.44; H, 3.48; N, 4.84. Found: C, 66.30; H, 3.46; N, 4.81.

2-Phenyl-3-(2-pyridyl)indole; Typical Procedure 1

A 100 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with **1a** (1.5 g, 5.19 mmol) in MeCN (30 mL) under argon. 2-Bromopyridine (0.742 mL, 7.78 mmol), $Pd(PPh_3)_4$ (0.299 g, 0.26 mmol), and Cs_2CO_3 (2.54 g, 7.78 mmol) were added under stirring. The reaction mixture was stirred at 100 °C until complete conversion (2 h, monitored by TLC analysis). After this time, the mixture was cooled to r.t., poured into EtOAc (350 mL) and washed with H_2O (3 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 85:15, Macherey-Nagel silica gel 60, 0.025–0.040 mm, 100 g) to yield 2-phenyl-3-(2-pyridyl)indole as a pale yellow powder; yield: 1.22 g (87%); mp 198–199 °C.

IR (KBr): 3366 (br), 1594 (m) cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 11.66 (s, 1 H), 8.58–8.71 (m, 1 H), 7.91 (d, *J* = 7.8 Hz, 1 H), 7.58–7.70 (m, 1 H), 7.27–7.58 (m, 6 H), 7.02–7.27 (m, 4 H).

^{13}C NMR (50.3 MHz, DMSO-d_6): δ = 155.0, 149.4, 136.4, 136.1, 136.0, 132.6, 128.7, 128.6, 128.1, 127.7, 123.9, 122.1, 120.6, 120.2, 120.0, 112.9, 111.4.

MS (EI, 70 eV): *m*/*z* (%) = 270 (M^+, 45), 269 (100).

Anal. Calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.35; H, 5.21; N, 10.33.

(2-Phenyl-1*H*-indol-3-yl)acetic Acid Ethyl Ester; Typical Procedure 2

A 250 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with **1a** (1.5 g, 5.19 mmol) in THF (60 mL). Ethyl iodoacetate (0.922 mL, 7.78 mmol), $Pd_2(dba)_3$ (0.119 g, 0.13

mmol), ttmpp (0.276 g, 0.52 mmol), and K_2CO_3 (2.15 g, 15.57 mmol) were added under argon. The reaction mixture was stirred at 80 °C for 3 h, until the disappearance of the starting alkyne (monitored by TLC analysis). After this time, the mixture was cooled to r.t., poured into EtOAc (350 mL), washed with 0.1 N HCl (10 mL) and H_2O (2 × 30 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 85:15, Macherey-Nagel silica gel 60, 0.025–0.040 mm, 100 g) to yield the indole product as a pale yellow oil; yield: 1.049 g (72%).

IR (neat): 3384 (br), 3061 (m), 2983 (m), 1704 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (s, 1 H), 7.75–7.67 (m, 3 H), 7.53–7.49 (m, 2 H), 7.47–7.35 (m, 2 H), 7.31–7.17 (m, 2 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.88 (s, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.3, 136.3, 135.9, 132.5, 129.2, 129.0, 128.4, 128.1, 122.6, 120.1, 119.4, 111.0, 105.8, 50.9, 31.3, 14.3.

MS (EI, 70 eV): *m*/*z* (%) = 279 (M^+, 38), 206 (100),

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.31; H, 6.11; N, 4.99.

2-Phenyl-3-cinnamylindole; Typical Procedure 3

A 100 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with **1a** (1.5 g, 5.19 mmol) in anhyd THF (30 mL). Cinnamyl carbonate (1.28 g, 6.22 mmol), $Pd(PPh_3)_4$ (0.299 g, 0.26 mmol), and K_2CO_3 (3.58 g, 25.95 mmol) were added under argon. The reaction mixture was stirred at 60 °C under argon for 3 h, until the disappearance of the trifluoroacetanilide (monitored by TLC analysis). Then, K_2CO_3 (3.58 g, 25.95 mmol) was added and the mixture was stirred at 80 °C for 24 h. The mixture was cooled to r.t., poured into EtOAc (350 mL) and washed with H_2O (3 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 95:5, Macherey-Nagel silica gel 60, 0.025–0.040 mm, 100 g) to yield the indole product as a yellow oil; yield: 1.49 g (93%).

IR (neat): 3416 (br), 3056 (m), 3025 (m), 2924 (w), 1457 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.69 (d, *J* = 7.9 Hz, 2 H), 7.62 (dd, J_1 = 7.1 Hz, J_2 = 1.3 Hz, 2 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 7.47–7.17 (m, 8 H), 6.58–6.51 (m, 2 H), 3.84 (d, *J* = 5.2 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 137.8, 136.1, 135.1, 133.0, 130.3, 129.8, 129.5, 129.0, 128.5, 128.0, 127.8, 127.0, 126.2, 122.5, 119.9, 119.6, 110.9, 110.7, 28.3.

MS (EI, 70 eV): *m*/*z* (%) = 309 (M^+, 100), 232 (16), 218 (62), 206 (58), 193 (14).

Anal. Calcd for $C_{23}H_{19}N$: C, 89.28; H, 6.19; N, 4.53. Found: C, 89.19; H, 6.17; N, 4.54.

2-Phenyl-3-(4-methoxybenzoyl)indole; Typical Procedure 4

A 250 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with **1a** (1.500 g, 5.19 mmol) in MeCN (60 mL). 4-Iodoanisole (1.821 g, 7.78 mmol), $Pd(PPh_3)_4$ (0.299 g, 0.26 mmol), and K_2CO_3 (3.581 g, 25.95 mmol) were added under argon. The flask was purged with CO for a few seconds, then connected to a balloon of CO (Ø = 230 mm) and stirred at 45 °C overnight. After this time, the mixture was cooled to r.t., poured into EtOAc (350 mL), washed with 0.1 HCl (10 mL) and H_2O (2 × 30 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 50:50, Macherey-Nagel silica gel 60, 0.025–0.040 mm, 100 g) to yield the indole product as a brown powder; yield: 1.018 g (60%); mp 153–155 °C.

IR (KBr): 3200 (m), 1590 (s) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.70 (br s, 1 H), 7.86–7.80 (m, 1 H), 7.69 (d, *J* = 8.9 Hz, 2 H), 7.45–7.36 (m, 3 H), 7.31–7.16 (m, 5 H), 6.7 (d, *J* = 8.9 Hz, 2 H), 3.78 (s, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): 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 (EI, 70 eV): *m*/*z* (%) = 327 (M^+, 88), 220 (100).

Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.54; H, 5.41; N, 4.52.

References

(1) For a recent review, see:Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
(2) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671.
(3) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915.
(4) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-WCH: Weinheim, **1998**, 203. (b) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 1; Negishi, E., Ed.; Wiley: New York, **2002**, 493.
(5) *o*-Ethynyltrifluoroacetanilide can be prepared in 70% overall yield from commercially available *o*-iodoaniline via a three-step process as described in Ref.[3]
(6) Cacchi, S.; Fabrizi, G.; Lamba, D.; Marinelli, F.; Parisi, L. M. *Synthesis* **2003**, 728.
(7) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363.
(8) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2000**, 394.
(9) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2000**, 647.
(10) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001.
(11) (a) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437. (b) See also: Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620. (c) See also: Arcadi, A.; Cacchi, S.; Cassetta, A.; Fabrizi, G.; Parisi, L. M. *Synlett* **2001**, 1605. (d) See also: Battistuzzi, G.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 1355.
(12) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841.
(13) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670.
(14) Colllini, M. D.; Ellingboe, J. W. *Tetrahedron Lett.* **1997**, *38*, 7963.