Synthesis of 2-Substituted Indoles via Pd/C-Catalyzed Reaction in Water[1]

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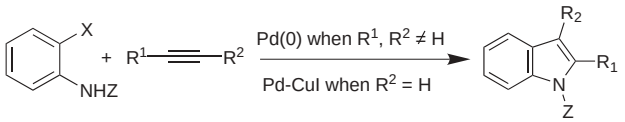
Abstract: A general and one-pot synthesis of 2-alkyl/aryl substituted indoles via a tandem Pd/C mediated coupling/5-*endo-dig* cyclization of terminal alkynes (including acetylenic carbinols) with *o*-iodoanilides in water is reported. The reaction is carried out using PPh_3 and CuI as co-catalysts and 2-aminoethanol as a base. The reaction appears to tolerate a variety of functional groups present in the alkynes and does not require the use of any organic co-solvent.

Key words: indoles, Sonogashira coupling/5-*endo-dig* cyclization, palladium catalyst, water

The indole nucleus is a frequently found unit in many natural products and diverse biologically active molecules.[2] Interesting pharmacological properties, such as antithrombotic,[3] anticancer,[4] histamine H_3 receptor antagonism[5] etc. exhibited by the various 2-substituted indoles have led to a continued interest in the practical synthesis of these compounds. Among the classical methods for the synthesis of indole ring, the Fischer indole synthesis, the Batcho–Leimgruber synthesis (from *o*-nitrotoluenes and dimethylformamide acetals), the Gassman synthesis (from *N*-haloanilines), the reductive cyclization of *o*-nitrobenzylketones and the Madelung cyclization of *N*-acyl-*o*-toluidines are often used. However, the introduction of an aryl group at the 2-position of an indole ring is usually achieved by de novo indole ring construction[6] either by Fischer indole synthesis or more popularly by transition metal mediated reactions,[7] especially by palladium catalyzed protocols.[8–10] Palladium-catalyzed annulation of *o*-haloanilines with terminal alkynes (under Sonogashira reaction conditions) or internal alkynes (under Larock's conditions) has been employed widely due to the versatile nature of these protocols, increased functional group tolerance and improved yields (Scheme 1). Despite being quite versatile, the synthesis of 2-substituted indoles employing terminal alkynes often involves a two-step process i.e. Sonogashira coupling of *o*-haloanilines with terminal alkynes followed by the cyclization of the resulting 2-alkynylanilines in the presence of various reagents (e.g. metal alkoxides, halides or Lewis acids).[11] Moreover, cyclization of anilides having an alkynol moiety at the 2-position yielded quinolines/2,3-dihydro-4(1*H*)-quinolones rather than indoles.[11d] Very recently, a one-pot synthesis of 2-substituted indoles has been reported in the presence of Pd(II)-NaY zeolite catalysts.[8a] However, the reaction was carried out in a sealed tube and appeared to be unsuitable for the preparation of these compounds in a large scale.



X = Br, I; Z = H, Alkyl, $COCH_3$, CO_2Et, SO_2CH_3, SO_2Ar, Boc

Scheme 1 Palladium-catalyzed synthesis of indoles

Palladium-promoted reactions in aqueous media are a focus of current research[12,13] because water-based synthetic processes are inherently safer as well as inexpensive (especially for industrial-scale processes). Therefore, the use of water-soluble catalysts[13g] and water-soluble phosphine ligands[13f] has been explored successfully. The use of Pd/C–CuI–PPh_3 as a catalyst system for efficient Sonogashira coupling has also been reported.[14,15] All these Pd-catalyzed reactions are usually carried out in an aqueous-organic media and a co-solvent such as acetonitrile[13f] or DME[15g] is often required. As part of our continuing interest in the utilization of palladium-catalyzed reactions[16] in aqueous media, we have developed a mild and efficient method for the synthesis of 2-substituted benzo[*b*]furans[17] via Pd/C-catalyzed C-C bond formation in water.[17a] This prompted us to investigate the feasibility of this methodology in the synthesis of indoles of potential pharmacological interest.[5,18] Herein, we report a straightforward and one-pot Pd/C-catalyzed synthesis of 2-substituted indoles in water.

Our earlier procedure for the synthesis of 2-substituted benzo[*b*]furans[17a] involves the use of an expensive and chiral amine base i.e. (*S*)-prolinol. In the search of an alternative but cheaper amine base for efficient coupling/5-*endo-dig* cyclization we were intrigued with the possibility of using 2-aminoethanol as a suitable replacement. Accordingly, we examined the reaction of *o*-iodoanilides **1** with terminal alkynes **2** in the presence of 2-aminoethanol in water (Table 1). Initially, we chose the reaction of *N*-trifluoroacetyl derivatives **1** of 2-iodoanilines (entries 1–3, Table 1) with phenylacetylene **2** to study the coupling/5-*endo-dig* cyclization in the presence of 10% Pd/C, PPh_3 and CuI as catalysts. Except in the case of 4-fluoro derivative **1c** the reaction did not afford good yields of the corresponding 2-substituted indoles. Moreover, deprotection of the trifluoroacetyl group occurred under these reaction conditions.[8a,i] Since the generation of N-protected indoles

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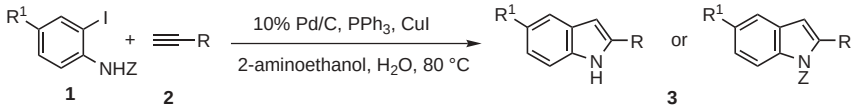
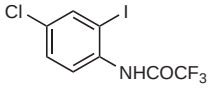
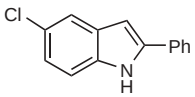
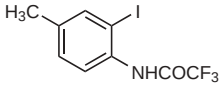
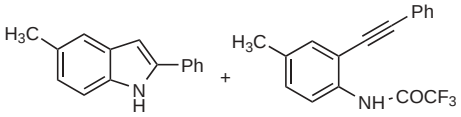
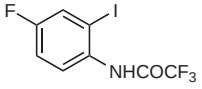
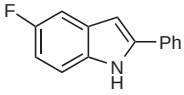
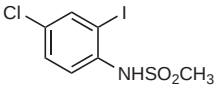
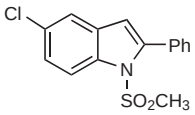
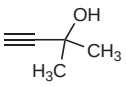
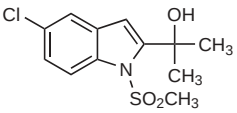
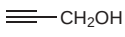
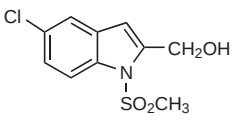
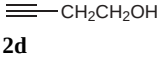
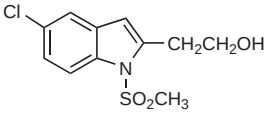
would allow us further functionalization of the indole nucleus we therefore, examined the reaction of *N*-methanesulfonyl derivative **1d** of 2-iodoanilines with terminal alkynes (entries 4–7, Table 1). The methanesulfonyl group was found to be stable under the present reaction conditions and the corresponding *N*-methanesulfonyl indoles **3d**–**g** were isolated in good yields. Using this optimized procedure we synthesized a number of 2-substituted 5-methylindoles[18b,c] **4** via palladium-catalyzed heteroannulation with Pd/C–CuI–PPh_3 as catalyst. Thus, when *o*-iodoanilide **1e**[8i,19a] was treated with 3 equivalents of terminal alkyne (**2**, R = alkyl, hydroxyalkyl etc.)[19b] in water in the presence of 10% Pd/C (0.03 equiv), PPh_3 (0.12 equiv), CuI (0.06 equiv) and 2-ethanolamine (3 equiv) under nitrogen, 2-substituted indoles **4** were obtained.[19c] The results are summarized in Table 2.

As can be seen from the Table 2, the heteroannulation of acetylenic compounds in a single synthetic operation afforded indoles **4** in good to excellent yields. By the use of this palladium-catalyzed reaction a variety of terminal acetylenes were reacted with *o*-iodoanilides (Table 2). Various substituents (including alkyl, hydroxyl, phenyl etc.) present in the acetylenic compounds **2** were well tolerated during the course of the reaction and yields were generally good irrespective of the nature of the substituents present in the acetylenic component (entries 1–8,

Table 1 Pd/C-Catalyzed Synthesis of 2-Substituted Indoles in Aqueous Media[a]



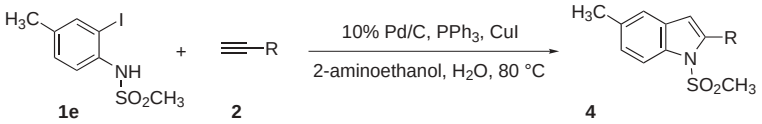
1 **2** **3**

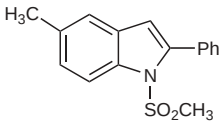
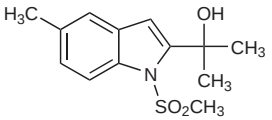
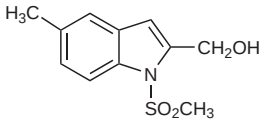
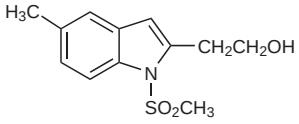
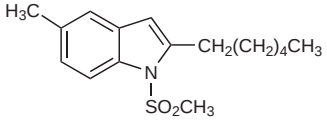
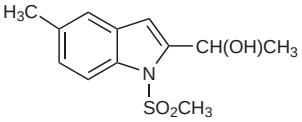
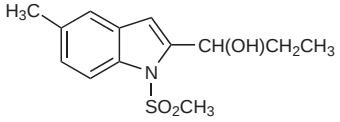
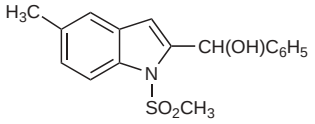
Entry	Aryl halide	Alkyne	Time (h)	Products[b] **3**	Yield (%)[c] of **3**
1	 **1a**	**2a**	4	 **3a**	40
2	 **1b**	**2a**	4	 **3b 5**	20[d]
3	 **1c**	**2a**	12	 **3c**	78
4	 **1d**	**2a**	4	 **3d**	62
5	**1d**	 **2b**	12	 **3e**	89
6	**1d**	 **2c**	12	 **3f**	65
7	**1d**	 **2d**	12	 **3g**	60

[a] All reactions were carried out by using **1** (1.0 equiv), **2** (3.0 equiv), 1:4:2 ratio of Pd/C:PPh_3:CuI, 2-aminoethanol (3 equiv) in H_2O.
[b] Identified by ^1H NMR, ^{13}C NMR, IR, MS.
[c] Isolated yields.
[d] Alkyne **5** was isolated in 35% yield.

Table 2). In contrast to the $Pd(PPh_3)_2Cl_2$-catalyzed reaction[11d] the present Pd/C–CuI–PPh_3 mediated coupling of *o*-iodoanilides with the acetylenic carbinols yielded the corresponding indole derivatives in good yields (e.g. entries 6–8, Table 2).[20] It is noteworthy that under the solvent-free conditions the reaction of *N*-(2-iodophenyl)methanesulfonamide with phenylacetylene in the presence of Pd–CuI–PPh_3/KF–Al_2O_3 yielded *N*-(*o*-ethynylphenyl)methanesulfonamide exclusively instead of the desired indole.[8i] Additional Pd(II) was required to obtain the desired indole derivative in this case.

Table 2 Pd/C-Catalyzed Synthesis of 2-Substituted *N*-Methylsulfonyl Indoles in Aqueous Media[a]



Entry	Alkyne	Time (h)	Products[b] **4**	Yield (%)[c] of **4**
1	—Ph **2a**	3	 **4a**	70
2	—$C(CH_3)_2OH$ **2b**	12	 **4b**	85
3	—CH_2OH **2c**	8	 **4c**	70
4	—CH_2CH_2OH **2d**	12	 **4d**	82
5	—$CH_2(CH_2)_4CH_3$ **2e**	48	 **4e**	40
6	—$CH(OH)CH_3$ **2f**	12	 **4f**	78
7	—$CH(OH)CH_2CH_3$ **2g**	12	 **4g**	80
8	—$CH(OH)C_6H_5$ **2h**	12	 **4h**	80

[a] All reactions were carried out by using **1e** (1.0 equiv), **2** (3.0 equiv), 1:4:2 ratio of Pd/C:PPh_3:CuI, 2-aminoethanol (3 equiv) in H_2O.
[b] Identified by ^1H NMR, ^{13}C NMR, IR, MS.
[c] Isolated yields.

Mechanistically, the reaction may proceed via in situ generation of a Pd(0) complex e.g. $L_2Pd(0)$ according to the typical Sonogashira pathway.[21a] However, the question arises as to whether palladium remains on the support or dissolves before the catalytically active species is formed. Recent studies[21b,c] have shown that a minor portion of the bound palladium (Pd/C) released into the solution is the actual catalytic species in such coupling reactions and Pd/C therefore serves as the source of the palladium. This also indicates that the catalytic cycle works in solution rather than on the surface and the active species is a dissolved Pd–PPh_3 complex.[21d] In the present case a 2-amino-ethanol-stabilized Pd(0)-complex perhaps catalyzes the reaction in aqueous media. Recent work by Amatore and Jutand provides strong evidence in support of the specific role played by halide ions to generate an anionic species such as $[L_2Pd(0)Cl]^-$.[22a–22c] In the present case, this anionic species is generated in situ from Pd/C and PPh_3 in the presence of CuI and presumably the 2-aminoethanol stabilized anionic species (**A**) facilitates the reaction in aqueous media due to its interaction with water molecules (via the hydroxyl group of the aminoethanol moiety of **A**).[16c] 2-Alkynylanilide thus obtained then undergoes transition metal promoted cyclization[7–10] to yield the 2-substituted indole.

In conclusion, we have described a palladium on carbon mediated practical synthesis of 2-alkyl/aryl substituted indoles in water in the presence of 2-aminoethanol. The present methodology is simple to perform, efficient and does not involve the use of expensive reagents or catalysts. Since water-based syntheses are safer and inexpensive, the described methodology will permit easy access to 2-substituted indoles not only for laboratory use but also for large-scale production. Some of the indoles synthesized were converted to compounds of potential biological significance.[23] Further application of this methodology for the generation of biologically interesting indole-based chemical libraries is under investigation.

Acknowledgment

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References

(1) DRL publication No 427.
(2) For a review, see: (a) Sundberg, R. J. *Pyrroles and their Benzo Derivatives: Synthesis and Applications*, In *Comprehensive Heterocyclic Chemistry*, Vol. 4; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, **1984**, 313–376. (b) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175.
(3) Young, W. B.; Kolesnikov, A.; Rai, R.; Sprengeler, P. A.; Leahy, E. M.; Shrader, W. D.; Sangalang, J.; Burgess-Henry, J.; Spencer, J.; Elrod, K.; Cregar, L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2253.
(4) Mackman, R. L.; Hui, H. C.; Breitenbucher, J. G.; Katz, B. A.; Luong, C.; Martelli, A.; McGee, D.; Radika, K.; Sendzik, M.; Spencer, J. R.; Sprengeler, P. A.; Tario, J.; Verner, E.; Wang, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2019.
(5) Chai, W.; Breitenbucher, J. G.; Kwok, A.; Li, X.; Wong, V.; Carruthers, N. I.; Lovenberg, T. W.; Mazur, C.; Wilson, S. J.; Axe, F. U.; Jones, T. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767.
(6) For a recent review on indole ring synthesis, see: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
(7) For Cu-mediated process, see: (a) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843. (b) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Perez, M.; Garcia-Martin, M. A.; Gonzalez, J. M. *J. Org. Chem.* **1996**, *61*, 5804. (c) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277.
(8) (a) Hong, K. B.; Lee, C. W.; Yum, E. K. *Tetrahedron Lett.* **2004**, *45*, 693. (b) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002**, *43*, 7699. (c) Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett.* **2001**, *42*, 5275. (d) Zhang, H. C.; Ye, H.; White, K. B.; Maryanoff, B. E. *Tetrahedron Lett.* **2001**, *42*, 4751. (e) Zhang, H. C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89. (f) Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307. (g) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915. (h) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 2225. (i) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017.
(9) (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Zhang, H.-C.; Brumfield, K. K.; Maryanoff, B. E. *Tetrahedron Lett.* **1997**, *38*, 2439. (d) Chen, C. Y.; Lieberman, D. R.; Larsen, R. D.; Reamer, R. A.; Verhoven, T. R.; Reider, P. J.; Cottrell, I. F.; Houghton, P. G. *Tetrahedron Lett.* **1994**, *35*, 6981. (e) Jeschke, T.; Wensbo, D.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 6471. (f) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.
(10) For Pd-mediated coupling reactions of haloindoles; see: (a) Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2000**, *41*, 8717. (b) Zhang, H.-C.; Ye, H.; White, K. B.; Maryanoff, B. E. *Tetrahedron Lett.* **2001**, *42*, 4751.
(11) (a) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305. (b) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539. (c) Mackman, R. L.; Katz, B. A.; Breitenbucher, J. G.; Hui, H. C.; Verner, E.; Luong, C.; Liu, L.; Sprengeler, P. A. *J. Med. Chem.* **2001**, *44*, 3856. (d) Kundu, N. G.; Mahanty, J. S.; Das, P.; Das, B. *Tetrahedron Lett.* **1993**, *34*, 1625. (e) For palladium mediated cyclization of 2-alkynylanilines see: Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662.
(12) (a) Leadbeater, N. E.; Marco, M.; Tominack, B. J. *Org. Lett.* **2003**, *5*, 3919. (b) *Aqueous-Phase Organometallic Catalysis, Concepts and Applications*; Cornils, B.; Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, **1998**.
(13) (a) Lopez-Deber, M. P.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, *3*, 2823. (b) Pierre Genet, J.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305. (c) Mori, A.; Ahmed, M. S. M.; Sekiguchi, A.; Masui, K.; Koike, T. *Chem. Lett.* **2002**, 756. (d) Bumagin, N. A.; Sukhomlinova, L. I.; Luzikova, E. V.; Tolstaya, T. P.; Beletskaya, I. P. *Tetrahedron Lett.* **1996**, *37*, 897. (e) Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71. (f) Amatore, C.; Blart, E.; Genet, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829. (g) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.*

1990, *112*, 4324. (h) Dibowski, H.; Schmidtchen, F. P. *Tetrahedron Lett.* **1998**, *39*, 525.

(14) De la Rosa, M. A.; Velarde, E.; Guzman, A. *Synth. Commun.* **1990**, *20*, 2059.

(15) (a) Novak, Z.; Szabo, A.; Repasi, J.; Kotschy, A. *J. Org. Chem.* **2003**, *68*, 3327. (b) For the use of Pd(OH)2/C as catalyst, see: Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571. (c) Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118. (d) Felpin, F.-X.; Vo-Thanh, G.; Villiéras, J.; Lebreton, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1121. (e) Bates, R. W.; Boonsombat, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 654. (f) Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, *63*, 1109. (g) Bleicher, L.; Cosford, N. D. P. *Synlett* **1995**, 1115. (h) Potts, K. T.; Horwitz, C. P.; Fessak, A.; Keshavarz, K. M.; Nash, K. E.; Toscano, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 10444.

(16) (a) Pal, M.; Parasuraman, K.; Subramanian, V.; Dakarapu, R.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2004**, *45*, 2305. (b) Pal, M.; Parasuraman, K.; Yeleswarapu, K. R. *Org. Lett.* **2003**, *5*, 349. (c) Pal, M.; Subramanian, V.; Parasuraman, K.; Yeleswarapu, K. R. *Tetrahedron* **2003**, *59*, 9563. (d) Pal, M.; Parasuraman, K.; Gupta, S.; Yeleswarapu, K. R. *Synlett* **2002**, 1976. (e) Pal, M.; Kundu, N. G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 449.

(17) (a) Pal, M.; Subramanian, V.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2003**, *44*, 8221. (b) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.* **1993**, 86. (c) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc., Chem. Commun.* **1992**, 41.

(18) (a) Radl, S.; Hezky, P.; Urbankova, J.; Vachal, P.; Krejci, I. *Collect. Czech. Chem. Commun.* **2000**, *65*, 280. (b) For biological activities of 5-methylindoles, see: Dai, J.; Sun, B.; Zhang, A.; Lin, K.; Wang, L. *Bull. Environ. Contam. Toxicol.* **1998**, *61*, 591. (c) Kon-Ya, K.; Shimidzu, N.; Miki, W.; Endo, M. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 2178. (d) For our recent synthesis of indole derivatives, see: Pal, M.; Dakarapu, R.; Padakanti, S. *J. Org. Chem.* **2004**, *69*, 2913.

(19) (a) *o*-Iodoanilides were prepared according to the procedure described in the literature, see: Xiao, W.-J.; Alper, H. *J. Org. Chem.* **1999**, *64*, 9646. (b) All the terminal alkynes used are commercially available. (c) **General Procedure for the Preparation of 2-Substituted Indoles(4):** A mixture of **1e** (1.60 mmol), 10% Pd/C (51 mg, 0.05 mmol), PPh_3 (50 mg, 0.19 mmol), CuI (18 mg, 0.09 mmol) and 2-aminoethanol (4.83 mmol) in H_2O (8 mL) was stirred at 25 °C for 1 h under nitrogen. The acetylenic compound **2** (4.00–5.00 mmol) was added slowly to the mixture with stirring. The reaction mixture was then stirred at 80 °C for the time indicated in Table 1. The mixture was cooled to r.t., diluted with EtOAc (120 mL) and filtered through celite. The filtrate was collected, washed with cold H_2O (2 × 75 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue thus obtained was purified by column chromatography (hexane–EtOAc) to afford the desired product.
Spectral and analytical data for **4a**: light brown solid; yield 70%; mp 128–130 °C (hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 1 H), 7.54 (d, *J* = 2.5 Hz, 1 H), 7.43–7.38 (m, 5 H), 7.19 (d, *J* = 8.4 Hz, 1 H), 6.65 (s, 1 H), 2.69 (s, 3 H, SO_2CH_3), 2.46 (s, 3 H, CH_3). MS (CI): *m/z* = 286 (100) [M + 1]. IR (neat): 1586.1, 1462.5, 1361.1 cm^{-1}. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.08, 136.24, 134.20, 131.99, 130.55, 129.96 (2 C), 128.68, 127.60 (2 C), 126.39, 120.88, 115.50, 112.98, 38.91 (SO_2CH_3), 21.18 (CH_3). HPLC: 97.3% [Symmetry Shield RP18 (250 × 4.6 mm), 0.01 M KH_2PO_4:MeCN, 1 mL/min 225 nm, retention time 13.7 min]. Elemental analysis found C, 67.39; H, 5.35; N, 4.89; $C_{16}H_{15}NO_2S$ requires C, 67.34; H, 5.30; N. 4.91%.
Compound **4g**: light brown solid; yield 80%; mp 78–80 °C (hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.7 Hz, 1 H), 7.34 (s, 1 H), 7.15 (d, *J* = 8.4 Hz, 1 H), 6.62 (s, 1 H), 5.02 (d, *J* = 7.9 Hz, 1 H), 3.09 (s, 3 H), 2.94 (d, *J* = 5.9 Hz, D_2O exchangeable, OH), 2.43 (s, 3 H), 2.07–1.97 (m, 2 H), 1.09 (t, *J* = 7.3 Hz, 3 H). MS (CI): *m/z* = 250 (100) [M$^+$ – OH]. IR (neat): 3540.1, 1462.4, 1358.0, 1159.6 cm^{-1}. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.42, 135.06, 133.29, 129.16, 126.19, 121.01, 113.67, 108.36, 67.76 (CHOH), 40.12 (SO_2CH_3), 28.59 (CH_2), 20.98 (CH_3), 10.53 (CH_3). HPLC: 99.3% [Inertsil ODS 3V (250 × 4.6 mm), 0.01 M KH_2PO_4 in MeCN, 1 mL/min, 220 nm, retention time 16.6 min]. Elemental analysis found C, 58.38; H, 6.40; N, 5.27; $C_{13}H_{17}NO_3S$ requires C, 58.40; H, 6.41; N. 5.24%.

(20) Although the methanesulfonyl group of iodoarene **1e** was tolerated under the present reaction conditions this group was removed efficiently from **4** using tetrabutylammonium fluoride in THF at elevated temperature to afford the corresponding indoles in good yields, see: Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595.

(21) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Novak, Z.; Szabo, A.; Repasi, J.; Kotschy, A. *J. Org. Chem.* **2003**, *68*, 3327. (c) Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571. (d) De la Rosa, M. A.; Velarde, E.; Guzman, A. *Synth. Commun.* **1990**, *20*, 2059.

(22) (a) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314. (b) Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168. (c) The anionic species generated from $Pd(PPh_3)_2Cl_2$ is thought to be the key intermediate and participates as active palladium species in these cross-coupling reactions, see: Grosshenny, V.; Romero, F. M.; Ziessel, R. *J. Org. Chem.* **1997**, *62*, 1491. (d) Amatore, C.; Jutand, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.

(23) Indole **4h** was converted to the corresponding ketone using MnO_2 in CH_2Cl_2 according to the procedure described in the literature. These ketones are of interest as analgesics.[18a] See: Jiang, J.; Gribble, G. W. *Synth. Commun.* **2002**, *32*, 2035.