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Tetrahedron
Tetrahedron 62 (2006) 3033–3039

Synthesis of 3,3′-disubstituted-2,2′-biindolyls through sequential palladium-catalysed reactions of 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide with organic halides/triflates

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Received 31 October 2005; revised 13 December 2005; accepted 12 January 2006

Available online 3 February 2006

Dedicated to the memory of Prof. Bianca Rosa Pietroni

Abstract—Palladium-catalysed reactions of aryl iodides/vinyl triflates with 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide provide a straightforward entry into 3,3′-disubstituted-2,2′-biindolyls. Subsequent application of the procedure to homochiral aryl iodides affords the corresponding chiral 3,3′-disubstituted-2,2′-biindolyls. The methodology can also be applied to the synthesis of benzo[*c*]indolo[2,3-*a*]carbazoles.

1. Introduction

Palladium-catalysed routes to heterocyclic compounds represent well-exploited synthetic approaches.[1] In particular, palladium-catalysed annulations involving both formation of carbon–carbon and carbon–nitrogen bonds, have proven to be very useful in the synthesis of a variety of heterocyclic systems.[2]

The aminopalladation/reductive elimination domino reaction of alkynes containing proximate nitrogen nucleophiles is a versatile synthetic methodology to build up complex indole and polycyclic indole derivatives.[3] The trifluoroacetamido group was shown to act as the proximate nitrogen nucleophile of choice for favouring palladium-catalysed cyclisations of *o*-alkynylaniline derivatives involving η^2-alkyne organopalladium intermediates. In addition, it allows the formation of free N–H indoles (the amide bond is broken during the reaction or/and the work-up), avoiding troublesome and time-consuming deprotection steps.[4]

This chemistry has been employed in the preparation of biologically active compounds.[5] It has also been adapted to a solid-supported synthesis for the preparation of combinatorial libraries of indoles with three variable components.[6]

However, while a variety of indole derivatives could be prepared in good to excellent yield by using aryl/vinyl halides/triflates as σ-donors,[7] the extension of the procedure to the synthesis of 3,3′-disubstituted-2,2′-biindolyl derivatives was limited to the synthesis of indolo[2,3-*a*]carbazole alkaloids[5c] by using *N*-benzyl-3,4-dibromomaleimide as the σ-donor. Products containing the biindolyl unit are of considerable interest, not only for their chemical architecture, but also due to their diverse pharmacological profiles.[8] Biindolyl-based red fluorescent materials have been prepared and used as non-doping red emitters.[9] The juxtaposition of the two nitrogens in 2,2′-biindolyls has also been exploited in the construction of various ligand systems.[10]

In connection with our current research interests in this area and in order to widen the scope and generality of the methodology, we decided to develop a procedure for the preparation of 3,3′-disubstituted-2,2′-biindolyl derivatives **3** through the palladium-catalysed reaction of readily

Keywords: Biindolyls; Palladium; Cyclisation; Aminopalladation/reductive elimination.
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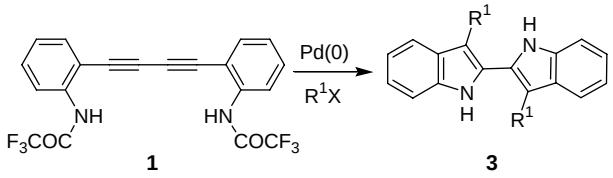
doi:10.1016/j.tet.2006.01.041

available 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide[5c] **1** with organic halides/triflates (Scheme 1). Despite its importance, synthetic methodologies for the construction of 3,3′-disubstituted-2,2′-biindolyl derivatives are scarce.[11]



Scheme 1.

Herein, we report the results of this study. The methodology was also applied to the synthesis of benzo[*c*]indolo[2,3-*a*]carbazole.

2. Results and discussion

Initial palladium-catalysed polyannulation attempts were focused on finding a general set of reaction conditions that could be used with a variety of aryl/vinyl halides/triflates. Based on the results obtained in the palladium-catalysed synthesis of 2,3-disubstituted indoles,[12] we initially examined the reaction of **1** (1 equiv) with aryl iodides (2.2 equiv) in the presence of $Pd(PPh_3)_4$ (0.05 equiv) and K_2CO_3 (5 equiv) in acetonitrile at 80 °C. Under these conditions, target 3,3′-disubstituted-2,2′-biindolyls **3a–e** can be prepared in satisfactory yields from aryl iodides **2a–e**, (Table 1, entries 1–5). As shown in Table 1, the reaction tolerates both electron-withdrawing or electron-donating substituents in the C_{sp2} donors. In a few cases, the 3-substituted biindolyls **5a–c** (Fig. 1) were also isolated in significant yields (Table 1, entries 6–9), and a tendency towards the production of 2,2′-biindolyl **4** (Fig. 1) was also observed (Table 1, entries 9 and 10).

Moreover, the 2,2′-biindol **4** was isolated as the main reaction product, when we extended the same procedure to include aryl bromides and aryl triflates (Table 1, entries 12 and 13). It was previously reported[7] that the reaction of *o*-alkynyltrifluoro-acetanilides with aryl bromides and triflates preferably afford 2-substituted 3-arylindoles rather than 2-substituted-indoles by increasing the temperature to 100 °C. However, when we tried to perform the reaction of **1** with **2j** and **2k** under the same reaction conditions we failed to obtain the corresponding derivatives **3b**,**f** in satisfactory yields and the cyclisation of **1** to **4** was a significant side reaction or even the main reaction path. Presumably, this different reactivity could be a consequence of higher acidity of **1** compared to that of *o*-alkynyltrifluoroacetanilides [calculations at the HF/4-31G+PCM show that ΔpK_a (H_2O) at 300 K between **1** and the *o*-ethynyltrifluoroacetanilide is $=-1.5$].[13]

Finally, when vinyl triflates were used as σ-donors, best results in the synthesis of the title derivatives **3** could be achieved by decreasing the reaction temperature at 45 °C (Table 1, entries 16 and 17).

The cyclisation of 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide **1** to give the 2,2′-biindolyl **4** involves a palladium-catalysed process rather than a base-promoted process. Thus, when **1** was reacted in CH_3CN at reflux for 24 h under the presence of $Pd(PPh_3)_4$ and K_2CO_3 the corresponding 2,2′-biindolyl **4** was isolated in 75% yield (the starting alkyne **1** was recovered in 21% yield). The involvement of a base-promoted cyclisation[14] of **1** to **4** could be ruled out since the starting reagent **1** was recovered (90% yield) when the same reaction was carried out omitting the palladium catalyst.

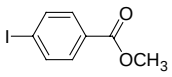
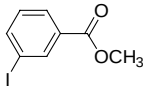
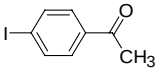
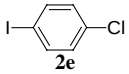
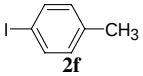
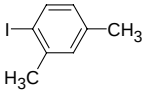
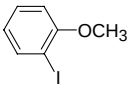
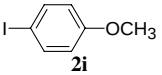
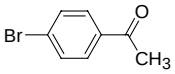
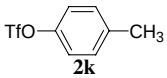
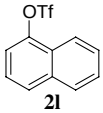
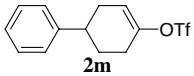
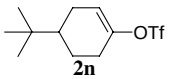
A plausible rationale, which accounts for the obtained results may involve two competing mechanisms. The sequential aminopalladation/reductive elimination reaction leading to the target derivatives **3** most probably proceeds through a mechanism most frequently found in the literature.[2d,e,3] Oxidative addition of palladium(0) in the aryl/vinyl halide/triflate bond affords a σ-organopalladium(II) intermediate, which can coordinate to the triple bond to give the η^2-alkyne-organopalladium intermediate **6**. The acetylene is then sufficiently electrophilic to undergo nucleophilic attack by the tethered nitrogen to give the σ-indolylpalladium complex **7** (5 *endo-dig* process). As far as the aniline moiety is concerned, no 3,3′-disubstituted-2,2′-biindolyl derivatives were obtained using the 2-[4-(2-aminophenyl)buta-1,3-diynyl]aniline containing free amino groups. Presumably, when carbon–carbon triple bonds are activated via coordination to organopalladiums, anionic nitrogen nucleophiles, or nitrogen atoms whose nucleophilic attack can be assisted by proton removal in the transition state leading to the aminopalladation adduct, are required to produce the desired cyclisation products.[12b] Reductive elimination of palladium(0) from the intermediate **7** regenerates the catalyst and affords product **3** after an iterative aminopalladation/reductive elimination reaction and protective group cleavage (Scheme 2).

Alternatively, a competitive oxidative addition of Pd(0) into the N–H bond of **1** to form a Pd–H species can take place under the reaction conditions. Then, intramolecular insertion of the triple bond can result in a 3-indolylpalladium derivative **8**. Sequential reductive elimination of the Pd–H intermediates/oxidative addition into N–H will provide 2,2′-biindolyl **4** (Scheme 3).

The activation of Pd(0) via oxidative addition into NH bond has been previously reported to take place with more acidic amides.[15] A similar mechanism has been suggested for the palladium-catalysed cyclisations of acetylene-containing *N*-protected α-aminoesters.[16] The formation of amido complexes directly from amines has also been observed.[17] Nevertheless, as demonstrated by the results obtained in the experiments performed in the presence either of Pd(II)[18] and Au(III),[19] a mechanism that leads to the 2,2′-biindolyl **4** involving a palladium catalyst that acts simultaneously[20] both as transition metal in the Pd(0) oxidation state and as Lewis acid in the Pd(II) oxidation state can not be ruled out.[21]

It is possible that the two different reaction paths afford the formation of derivative **5** when operating together.

Table 1. Synthesis of 2,2′-biindolyls **3**

Entry	σ-Donor **2**	Time (h)	**3** (%)[a,b]	**4** (%)[a,b]	**5** (%)[a,b]
1	 **2a**	24	**3a** 82	—	—
2	 **2b**	3.5	**3b** 77	—	—
3	 **2c**	4	**3c** 63	—	—
4	 **2d**	24	**3d** 73	—	—
5	 **2e**	1.5	**3e** 82	—	—
6	 **2f**	16	**3f** 50	—	**5a** 47
7	**2f**	4	**3f** 79[c]	—	**5a** 14[c]
8	 **2g**	4.5	**3g** 23	—	**5b** 67
9	 **2h**	24	**3h** 38	23	**5c** 30
10	 **2i**	17	**3i** 75	15	—
11	**2i**	2	**3i** 90[c]	—	—
12	 **2j**	24	**3b** 15[d]	65[d]	—
13	 **2k**	16	**3f** 15[e]	33[e]	—
14	**2k**	16	**3f** 34[f]	—	—
15	 **2l**	24	**3j** 51[g]	—	—
16	 **2m**	4	**3k** 45[g]	—	—
17	 **2n**	5	**3l** 61[g]	—	—

[a] Yields refer to single runs and are given for isolated products.
[b] Unless otherwise stated, reactions were carried out under a nitrogen atmosphere according to the following procedure: **1/2**/K_2CO_3/$Pd(PPh_3)_4$ = 1:2.2:5:0.07 in CH_3CN at 80 °C (0.12–0.35 mmol scale).
[c] Reaction was carried out at 80 °C in CH_3CN under a nitrogen atmosphere using the following molar ratios: **1/2**/K_2CO_3/$Pd(PPh_3)_4$ = 1:4.4:5:0.07.
[d] The reaction was carried out in CH_3CN at 100 °C under a nitrogen atmosphere using the following molar ratios: **1/2c**/Cs_2CO_3/$Pd(PPh_3)_4$ = 1:3:3:0.07.
[e] The reaction was carried out in CH_3CN at 100 °C under a nitrogen atmosphere using the following molar ratios: **1/2g**/Cs_2CO_3/$Pd(PPh_3)_4$ = 1:2.2:3:0.07.
[f] The reaction was carried out in CH_3CN at 100 °C under a nitrogen atmosphere using the following molar ratios: **1/2g**/Cs_2CO_3/$Pd(PPh_3)_4$ = 1:3:3:0.07.
[g] The reaction was carried out in CH_3CN at 45 °C under a nitrogen atmosphere using the following molar ratios: **1/2**/K_2CO_3/$Pd(PPh_3)_4$ = 1:2.2:3:0.07.

The feature of the σ-donor **2**, the reaction temperature and the **1**:σ-donor ratio were found to play a pivotal role in controlling the balance of the reaction paths. The preferential formation of 2,2′-biindolyl **4** is observed when aryl bromides/triflates are used as σ-donor precursors. Apparently, at the temperature of 80 °C the oxidative addition of aryl bromides/triflates is relatively slow and the cyclisation of **1** to **4** is the main reaction. According to that

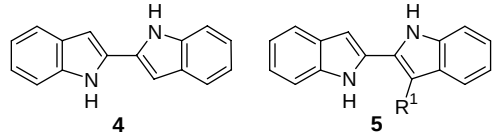
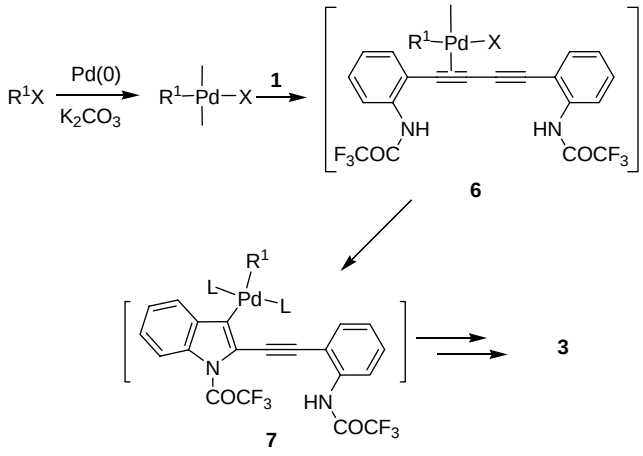
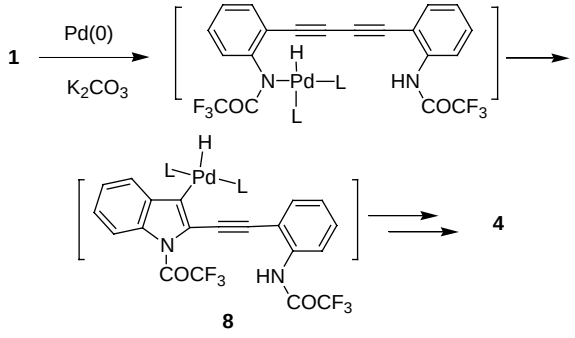


Figure 1.



Scheme 2.

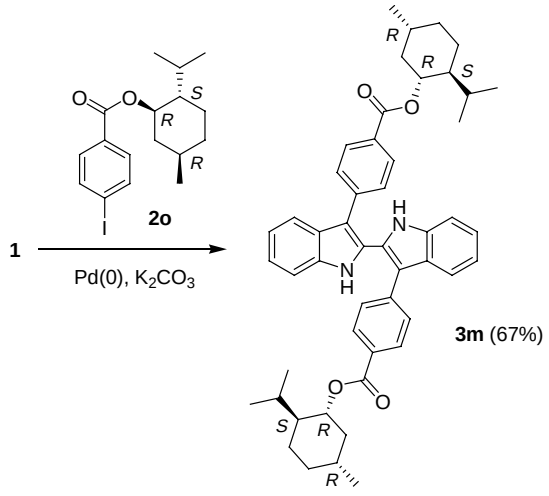


Scheme 3.

the reaction of **1** with the 5-bromopyrimidine under the same reaction conditions used for aryl iodides led only to the formation of **4** (75% yield). However, under the conditions previously reported to successfully give 2-substituted 3-aryl- and 3-heteroarylindoles by the palladium-catalysed reaction of *o*-alkynyltrifluoroacetanilides with aryl bromides and triflates[7] the formation of **3** was disappointing from a synthetic point of view (Table 1, entries 12 and 13). Very likely, at 100 °C the oxidative addition of Pd(0) into the N–H bond is the fastest process. According to that the formation of the 2,2′-biindolyl **4** was the main reaction product (88% yield) when **1** was reacted with the more reactive vinyl triflate **2m** in CH_3CN at 100 °C in the presence of $Pd(PPh_3)_4$ and K_2CO_3. Consequently, we failed to shift the reaction towards the aminopalladation/reductive elimination mechanism when aryl/heteroaryl bromides were used as σ-donors, even if the formation of the target derivatives **3** can be achieved in moderate yield by increasing the **1**:**2** molar ratio (Table 1, entry 14).

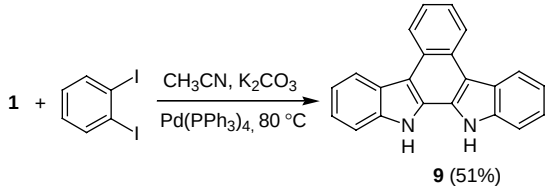
The increasing of the 1:2 molar ratio also limited the formation of the derivates **5** (Table 1, entries 7 and 11).

Interestingly, application of the procedure to (−)-menthyl *p*-iodobenzoate **2o** (Scheme 4) and (+)-menthyl *p*-iodobenzoate **2o′** led to the formation in good yields of corresponding chiral 3,3′-disubstituted-biindolyls **3m** (67% yield) and **3m′** (61% yield) derivatives, respectively. The absolute stereochemistry of **3m** and **3m′** can be assigned on the assumption that the stereogenic centres in the starting aryl iodide are not affected during this transformation.



Scheme 4.

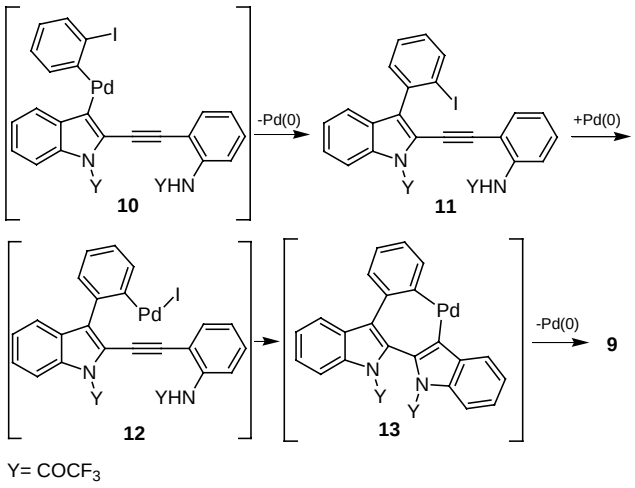
Moreover, treating **1** with 1,2-diiodobenzene provides an easy entry into the benzo[*c*]indolo[2,3-*a*]carbazole **9** (Scheme 5).



Scheme 5.

To the best of our knowledge, the synthesis of this heterocyclic system has not been reported previously. Intermediates **10**–**13** are suggested to be involved in a palladium(0)/palladium(II) catalytic cycle (Scheme 6).

In conclusion, because of the simple experimental procedure, easy availability of starting materials, and ability to incorporate a variety of functional groups, the present methods represents a valuable tool for the synthesis of 3,3′-disubstituted-2,2′-biindolys through the palladium-catalysed reaction of 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide with aryl iodides/vinyl triflates. Subsequent application of the procedure to homochiral aryl iodides affords the corresponding chiral 3,3′-disubstituted-2,2′-biindolys. It is worth noting that the here reported protocol could allow a versatile access to indolobenzocarbazole fused derivatives from 1,2-diiodoarenes.



Scheme 6.

3. Experimental

3.1. General

Temperatures are reported as bath temperature. Solvents used in extraction and purification were distilled prior to use. Compounds were visualised on analytical thin-layer chromatograms (TLC) by UV light (254 nm). The products, after usual work-up, were purified by flash chromatography on silica gel (230–400 mesh) eluting with *n*-hexane/ethyl acetate mixtures. ^{1}H and ^{13}C NMR spectra were recorded with a Varian-Gemini at 200 MHz and a Bruker AC 200 E spectrometers. ESI mass spectra were recorded with a ThermoFinnigan LCQ Deca XP Plus equipped with an orthogonal ESI source and ESI accurate mass measurements were recorded with a Mass spectrometer Finnigan TSQ Quantum Ultra with accurate mass options instrument. IR were recorded with Perkin-Elmer 683 and 16 PC spectrometers. Only the most significant IR absorptions are given. Optical rotations were measured on a Perkin Elmer 343 plus polarimeter. CHN analyses were recorded with an Eager 200 analyser. All starting materials, catalysts, and solvents if not otherwise stated, are commercially available and were used as purchased, without further purification. The 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide[5c] **1**, triflates[22] **2f**, **l**–**n**, (−)-menthyl *p*-iodobenzoate[23] **2o** and (+)-menthyl *p*-iodobenzoate were prepared according to described methods. The following products were identified by comparison of their physical and spectral data with those given in the cited references: 2,2′biindolyl[14b] **4** and 3,3′-diphenyl-1*H*,1′*H*-[2,2′]biindolyl[11a] **3a**.

3.1.1. General procedure for the preparation of 3,3′-disubstituted-2,2′-biindolys 3. A typical procedure is as follows: to a stirred solution of 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide **1** (0.150 g, 0.35 mmol) in boiling acetonitrile (7 mL) were added methyl 4-iodobenzoate **2b** (0.195 g, 0.78 mmol), K_2CO_3 (0.244 g, 1.77 mmol) and $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol). The reaction mixture was stirred at 80 °C (bath temperature) under a nitrogen atmosphere for 3.5 h and poured in a separatory funnel containing water 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 0.117 g (77%) of **3b**: Yellow solid; IR (KBr) 3340, 1720, 1610, 770, 740 cm^{-1}; ^{1}H NMR (DMSO) δ 3.74 (s, 6H), 7.05–7.20 (m, 8H), 7.45–7.56 (m, 8H), 11.83 (s, 2H); ^{13}C NMR δ 57.9, 117.9, 121.0, 124.4, 126.1, 128.5, 132.1, 132.6, 133.0, 134.3, 135.4, 135.5, 139.3, 141.2, 142.6, 172.1; ESI-MS: *m*/*z* (% relative intensity) 499.3 (93) $(M-H)^-$; ESI-HRMS calcd for $C_{32}H_{23}N_2O_4$ 499.544, Found 499.541.

3.1.2. 3,3′-Bis-(3-benzoic acid methyl ester)-1*H*,1′*H*-[2,2′]biindolyl 3c. Yield: 144.0 mg, 63%; Yellow solid; IR (KBr) 3320, 1710, 860 cm^{-1}; ^{1}H NMR (DMSO) δ 3.74 (s, 6H), 7.06–7.20 (m, 8H), 7.45–7.56 (m, 8H), 11.83 (br s, 2H); ^{13}C NMR (DMSO) δ 57.9, 117.9, 121.0, 124.4, 126.1, 128.5, 132.1, 132.6, 133.0, 134.4, 135.4, 135.5, 139.3, 141.2, 142.6, 172.0. Anal. Calcd for $C_{32}H_{24}N_2O_4$ C, 76.78; H, 4.83; N, 5.60; Found C, 76.63; H, 4.86; N, 5.55.

3.1.3. 1-{4-[3′-(4-Acetyl-phenyl)-1*H*,1′*H*-[2,2′]biindolyl-3-yl]-phenyl}-ethanone 3d. Yield: 166.0 mg, 73%; Yellow solid; IR (KBr) 3320, 1740, 730 cm^{-1}; ^{1}H NMR (DMSO) δ 2.50 (s, 6H), 7.06–7.21 (m, 6H), 7.19 (d, J=8.3 Hz, 4H), 7.48 (d, J=7.7 Hz, 2H), 7.64 (d, J=8.3 Hz, 4H), δ 11.64 (br s, 2H); ^{13}C NMR δ 26.4, 111.8, 115.3, 118.8, 120.2, 122.5, 126.5, 127.4, 127.9, 128.5, 133.7, 136.7, 140.2, 196.8; ESI-MS: *m*/*z* (% relative intensity) 467.4 (100) $(M-H)^-$; ESI-HRMS calcd for $C_{32}H_{23}N_2O_2$ 467.551, Found 467.553.

3.1.4. 3,3′-Bis-(4-chloro-phenyl)-1*H*,1′*H*-[2,2′]biindolyl 3e. Yield: 172.0 mg, 82%; Yellow solid; IR (KBr) 3425, 1620, 1020, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.95–7.26 (m, 12H), 7.36–7.46 (m, 2H), 7.54–7.61 (m, 2H), 11.69 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 111.8, 114.6, 118.6, 120.0, 122.4, 126.4, 126.8, 127.6, 130.1, 133.6, 136.5; ESI-MS: *m*/*z* (% relative intensity) 453.4 (65) $(M-H)^-$, 451.4 (100) $(M-H)^-$. Anal. Calcd for $C_{28}H_{18}Cl_2N_2$ C, 74.18; H, 4.00; N, 6.18; Found C, 74.05; H, 4.16; N, 6.25.

3.1.5. 3,3′-Di-*p*-tolyl-1*H*,1′*H*-[2,2′]biindolyl 3f. Yield: 148.0 mg, 79%; Yellow solid; IR (KBr) 3300, 1520, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 6H), 7.08–7.28 (m, 6H), 7.26 (d, J=7.9 Hz, 4H), 7.48 (d, J=7.9 Hz, 4H), 7.60 (d, J=7.3 Hz, 2H), 8.05 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 110.8, 115.6, 119.4, 120.2, 122.9, 125.9, 127.9, 129.7, 130.1, 131.3, 135.8, 136.8. Anal. Calcd for $C_{30}H_{24}N_2$ C, 87.35; H, 5.86; N, 6.79; Found C, 87.40; H, 5.68; N, 6.89.

3.1.6. 3,3′-Bis-(2,4-dimethyl-phenyl)-1*H*,1′*H*-[2,2′]biindolyl 3g. Yield: 100.0 mg, 23%; Dark brown solid; IR (KBr) 3480, 750 cm^{-1}; ^{1}H NMR (DMSO) δ 2.21 (s, 6H), 2.22 (s, 6H), 6.46 (d, J=7.7 Hz, 1H), 6.58–6.68 (m, 3H), 6.79 (s, 2H), 6.091–7.16 (m, 6H), 7.44 (d, J=8.0 Hz, 2H), 11.48 (br s, 1H), 11.55 (br s, 1H); ^{13}C NMR (DMSO) δ 19.8, 20.8, 111.4, 115.6, 116.1, 119.0, 121.6, 125.5, 125.6, 127.7, 130.0, 130.2, 130.4, 136.0, 136.1, 136.7; ESI-MS: *m*/*z* (% relative intensity) 439.6 (94) $(M-H)^-$, ESI-HRMS calcd for $C_{32}H_{27}N_2$ 439.579, Found 439.577.

3.1.7. 3,3′-Bis-(2-methoxy-phenyl)-1*H*,1′*H*-[2,2′]biindolyl 3h. Yield: 84.0 mg, 38%; Dark brown solid; IR (KBr) 3490, 750 cm^{-1}; ^1H NMR (DMSO) δ 3.40 (s, 6H), 6.65–6.70 (m, 2H), 6.80–6.82 (m, 2H), 6.98–7.186 (m, 8H), 7.39 (d, $J=8.0$ Hz, 4H), 11.30 (br s, 2H); ^{13}C NMR (DMSO) δ 55.1, 100.3, 111.2, 116.4, 126.9, 127.7, 128.1, 128.8, 131.1, 136.0, 156.7, 157.6. Anal. Calcd for $C_{30}H_{24}N_2O_2$ C, 81.06; H, 5.44; N, 6.30; Found C, 81.04; H, 5.71; N, 6.27.

3.1.8. 3,3′-Bis-(4-methoxy-phenyl)-1*H*,1′*H*-[2,2′]-biindolyl 3i. Yield: 108.0 mg, 75%; Brown solid; IR (KBr) 3300, 1730, 820 cm^{-1}; ^1H NMR (DMSO) δ 3.60 (s, 6H), 6.69 (d, $J=8.3$ Hz, 4H), 6.93–7.12 (m, 8H), 7.32 (d, $J=7.6$ Hz, 2H), 7.54 (d, $J=7.6$ Hz, 2H), 11.37 (br s, 2H); ^{13}C NMR (DMSO) δ 54.9, 111.6, 113.8, 115.8, 118.9, 119.5, 122.0, 126.5, 126.7, 127.2, 129.5, 136.2, 157.3; ESI-MS: *m/z* (% relative intensity) 445.3 (100) $(M+H)^+$, 339.3 (84); ESI-HRMS calcd for $C_{30}H_{25}N_2O_2$ 445.540, Found 445.535.

3.1.9. 3,3′-Di-naphthalen-1-yl-1*H*,1′*H*-[2,2′]biindolyl 3j. Yield: 120.0 mg, 51%; Dark brown solid; IR (KBr) 3200, 740 cm^{-1}; ^1H NMR (DMSO) δ 6.51–7.63 (m, 22H), 7.86 (d, $J=8.6$ Hz, 2H), 11.64 (br s, 2H); ^{13}C NMR δ 101.4, 111.8, 113.9, 118.7, 119.4, 119.9, 120.0, 121.7, 122.4, 125.1, 126.1, 126.7, 127.3, 127.6, 127.8, 128.1, 128.5, 131.3, 132.5, 136.5; ESI-MS: *m/z* (% relative intensity) 483.4 (100) $(M-H)^-$, ESI-HRMS calcd for $C_{36}H_{23}N_2$ 483.592, Found 483.589.

3.1.10. 3,3′-Bis-(4-phenyl-cyclohex-1-enyl)-1*H*,1′*H*-[2,2′]biindolyl 3k. Yield: 86.0 mg, 45%; Brown solid; IR (KBr) 3180, 1480, 740 cm^{-1}; ^1H NMR (DMSO) δ 1.85–1.95 (m, 4H), 2.03–2.07 (m, 4H), 2.53–2.59 (m, 6H), 6.15 (br s, 2H), 7.05–7.49 (m, 16H), 7.76 (d, $J=7.6$ Hz, 2H), 10.35 (br s, 2H); ^{13}C NMR (DMSO) δ 28.9, 30.0, 34.2, 111.4, 117.8, 119.5, 121.8, 125.9, 126.6, 126.7, 126.9, 128.4, 131.5, 136.0, 136.3, 147.0; ESI-MS: *m/z* (% relative intensity) 543.4 (100) $(M-H)^-$, ESI-HRMS calcd for $C_{40}H_{35}N_2$ 543.731, Found 543.730.

3.1.11. 3,3′-Bis-(4-*tert*-butyl-cyclohex-1-enyl)-1*H*,1′*H*-[2,2′]biindolyl 3l. Yield: 150.0 mg, 61%; Yellow solid; IR (KBr) 3415, 1614, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 18H), 1.01–1.55 (m, 6H), 1.93–2.05 (m, 4H), 2.35 (br s, 4H), 6.10 (m, 2H), 7.08–7.25 (m, 4H), 7.33 (d, $J=7.3$ Hz, 2H), 7.59 (d, $J=7.7$ Hz, 2H), 8.71 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 25.1, 27.5, 27.8, 31.7, 32.6, 44.4, 110.9, 117.6, 119.8, 120.0, 122.8, 126.3, 128.3, 129.6, 132.9, 135.9; ESI-MS: *m/z* (% relative intensity) 505.5 (43) $(M+H)^+$, 504.4 (100) $(M)^+$, 503.3 (73) $(M-H)^+$, 367 (21). Anal. Calcd for $C_{36}H_{44}N_2$ C, 85.66; H, 8.79; N, 5.55; Found C, 85.49; H, 8.73; N, 5.58.

3.1.12. (−)-3,3′-Bis[benzoic(1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexyl ester]-1*H*,1′*H*-[2,2′]biindolyl 3m. Yield: 216.0 mg, 67%; Yellow solid; $[\alpha]_D$ −20.8 (5.45 mg/mL, $CHCl_3$); IR (KBr) 3350, 1720, 1600, 1270, 740 cm^{-1}; ^1H NMR (DMSO) δ 0.83 (d, $J=5.8$ Hz, 6H), 0.89 (d, $J=3.6$ Hz, 6H), 0.93 (d, $J=4.1$ Hz, 6H), 1.02–2.13 (m, 18H), 4.85–5.04 (m, 2H), 7.13–7.24 (m, 6H), 7.52 (d, $J=8.3$ Hz, 4H), 7.72 (d, $J=8.0$ Hz, 2H), 7.98 (d, $J=8.3$ Hz, 4H), 8.46 (br s, 2H); ^{13}C NMR (DMSO) δ 16.5, 20.8, 22.0, 23.6, 26.5, 31.4, 34.3, 40.9, 42.2, 74.9, 111.4, 115.7, 119.4, 120.9, 123.5, 126.3, 127.2, 128.6, 129.5, 130.0, 136.3, 139.1, 166.1; ESI-MS: *m/z* (% relative intensity) 749.2 (100) $(M+H)^+$. Anal. Calcd for $C_{50}H_{56}N_2O_4$ C, 80.18; H, 7.54; N, 3.74; Found C, 80.15; H, 7.48; N, 7.60.

3.1.13. (+)-3,3′-Bis[benzoic(1*S*,2*R*,5*S*)-2-isopropyl-5-methyl-cyclohexyl ester]-1*H*,1′*H*-[2,2′]biindolyl 3m′. Yield: 468.0 mg, 61%; Yellow solid; $[\alpha]_D$ +20.5 (5.24 mg/mL, $CHCl_3$).

3.1.14. 3-*p*-Tolyl-1*H*,1′*H*-[2,2′]biindolyl 5a. Yield: 20.0 mg, 14%; Brown solid; IR (KBr) 3400, 820 cm^{-1}; ^1H NMR (DMSO) δ 2.37 (s, 3H), 6.48 (s, 1H), 6.98–7.49 (m, 12H), 11.06 (br s, 1H), 11.48 (br s, 1H); mass spectrum (EI): *m/z* (% relative intensity) 323 (100) $(M+H)^+$, Anal. Calcd for $C_{23}H_{18}N_2$ C, 85.68; H, 5.63; N, 8.69; Found C, 85.70; H, 5.82; N, 8.57.

3.1.15. 3-(2,4-Dimethyl-phenyl)-1*H*,1′*H*-[2,2′]biindolyl 5b. Yield: 222.0 mg, 67%; Dark yellow solid; IR (KBr) 3490, 750 cm^{-1}; ^1H NMR (DMSO) δ 1.97 (s, 3H), 2.38 (s, 3H), 6.10 (s, 1H), 6.94–7.19 (m, 9H), 7.37–7.50 (m, 6H), 10.99 (br s, 1H), 11.38 (br s, 1H); ^{13}C NMR (DMSO) δ 19.6, 20.8, 100.0, 111.2, 113.5, 118.6, 119.4, 119.6, 119.8, 121.5, 121.9, 126.7, 127.2, 128.1, 128.7, 130.7, 130.9, 131.1, 131.3, 135.7, 136.1, 136.3, 136.9; (EI): *m/z* (% relative intensity) 337 (100) $(M+H)^+$, 322 (34). Anal. Calcd for $C_{24}H_{20}N_2$ C, 85.68; H, 5.99; N, 8.33; Found C, 85.59; H, 5.84; N, 8.41.

3.1.16. 3-(2-Methoxy-phenyl)-1*H*,1′*H*-[2,2′]biindolyl 5c. Yield: 36.0 mg, 30%; Yellow solid; ^1H NMR (DMSO) δ 3.60 (s, 3H), 6.60–7.41 (m, 13H), 10.95 (br s, 11.35H); EI-MS: *m/z* (% relative intensity) 339.2 (100) $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{19}N_2O$ 339.409, Found 339.405.

3.1.17. Experimental procedure for the preparation of benzo[*c*]indolo[2,3-*a*]carbazole 9. To a stirred solution of 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide **1** (0.100 g, 0.24 mmol) in acetonitrile/DMSO (7 mL/1 mL) were added 1,2-diiodobenzene (0.093 g, 0.28 mmol), K_2CO_3 (0.099 g, 0.72 mmol) and $Pd(PPh_3)_4$ (0.019 g, 0.017 mmol). The reaction mixture was stirred at 80 °C (bath temperature) under a nitrogen atmosphere for 20 h and poured in a separatory funnel containing water 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 75:25 *n*-hexane/EtOAc mixture to give 0.037 g (51%) of **9**: Dark solid; IR (KBr) 3450, 820, 750 cm^{-1}; ^1H NMR (DMSO) δ 6.81–6.84 (m, 4H), 7.06–7.10 (m, 2H), 7.24–7.28 (d, $J=8.0$ Hz, 2H), 8.04–8.08 (d, $J=8.0$ Hz, 2H), 8.32–8.36 (m, 2H), 11.01 (s, 2H); ^{13}C NMR δ 112.1, 113.2, 119.0, 120.1, 121.2, 121.6, 123.6, 123.8, 125.8, 126.3, 138.4; ESI-MS *m/z* (% relative intensity) 329.2 (100) $(M+Na)^+$ ESI-HRMS calcd for $C_{22}H_{14}N_2Na$ 329.357, Found 329.353.

Acknowledgements

Support from FIRB 2001 (RBAU01FEPP), and the Università degli studi dell'Aquila are gratefully acknowledged

References and notes

1. (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley Interscience: New York, 2002. (d) Lee, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry*; Baldwin, J. E., Williams, R. M., Eds.; Elsevier Science: Oxford, UK, 2000.
2. (a) Kirsch, G.; Hesse, S.; Comel, A. *Curr. Org. Synth.* **2004**, *1*, 47–63. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Tetrahedron Lett.* **2004**, *45*, 2431–2434. (c) Bacchi, A.; Costa, M.; Della Cà, N.; Fabbricatore, M.; Fazio, A.; Gabriele, B.; Nasi, C.; Salerno, G. *Eur. J. Org. Chem.* **2004**, 574–585. (d) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111. (e) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115–2134. (f) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920–928. (g) Rossi, E.; Abbiati, G. In Attanasi, O. A., Spinelli, D., Eds.; Targets in Heterocyclic Systems; Italian Society of Chemistry: Rome, 2003; Vol. 7, pp 87–107.
3. (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (b) Cacchi, S.; Fabrizi, G.; Battistuzzi, G. *Eur. J. Org. Chem.* **2002**, 2671–2681. (c) Cacchi, S.; Marinelli, F. In Negishi, E., Ed.; Handbook of Organopalladium Chemistry for Organic Synthesis; Wiley: New York, 2002; Vol. 2, pp 2227–2244.
4. Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *J. Org. Chem.* **2005**, *70*, 6213–6227 and references therein.
5. (a) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670–2673. (b) McGuinan, C.; Brancale, A.; Barucki, H.; Srinivasan, S.; Jones, G.; Pathirana, R.; Carangio, A.; Blewett, S.; Luoni, G.; Bidet, O.; Andrei, G.; Snoek, R.; De Clercq, E.; Balzarini, J. *Antiviral Chem. Chemother.* **2001**, *12*, 77–89. (c) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *35*, 7841–7844.
6. Collini, M. D.; Ellingboe, J. W. *Tetrahedron Lett.* **1997**, *38*, 7963–7966.
7. (a) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Synthesis* **2004**, 1889–1894. (b) Cacchi, S.; Fabrizi, G.; Lamba, D.; Marinelli, F.; Parisi, L. M. *Synthesis* **2003**, 728–734.
8. (a) Saulnier, M. G.; Langley, D. R.; Frennesson, D. B.; Long, B. H.; Huang, S.; Gao, Q.; Wu, D.; Fairchild, C. R.; Ruediger, E.; Zimmermann, K.; St. Laurent, D. R.; Balasubramanian, B. N.; Vyiaa, D. M. *Org. Lett.* **2005**, *7*, 1271–1274. (b) Aubry, C.; Patel, A.; Mahale, S.; Chaudhuri, B.; Maréchal, J.-D.; Sutcliffe, M. J.; Jenkins, P. R. *Tetrahedron Lett.* **2005**, *46*, 1423–1425. (c) Garg, N.; Stoltz, B. M. *Tetrahedron Lett.* **2005**, *46*, 1997–2000. (d) Kam, T.-O.; Choo, Y.-M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 3957–3966. (e) Santos, M. M. M.; Lobo, A. M.; Prabhakar, S.; Marques, M. M. B. *Tetrahedron Lett.* **2004**, *45*, 2347–2349. (f) Faul, M.; Engler, T. A.; Sullivan, K. A.; Grutsch, J. L.; Clayton, M. T.; Martinelli, M. J.; Pawlak, J. M.; LeTourneau, M.; Coffey, D. S.; Pedersen, S. W.; Kolis, P.; Furness, K.; Malhotra, S.; Al-awar, R. M.; Ray, J. E. *J. Org. Chem.* **2004**, *69*, 2967–2975. (g) Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3721–3723. (h) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641–9651.
9. Fang, Q.; Xu, B.; Jiang, B.; Fu, H.; Chen, X.; Cao, A. *J. Chem. Soc.* **2005**, 1468–1470.
10. Black, D. St. C. *Synlett* **1993**, 246–252.
11. (a) Fürster, A.; Ptock, A.; Weintritt, H.; Goddard, R.; Krüger, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 678–681. (b) Bergman, J.; Kock, E.; Pelcman, B. *Tetrahedron* **1995**, *51*, 5631–5642 and references therein.
12. (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915–3918. (b) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437–452.
13. Aschi, M., Unplubished results.
14. (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Heterocycles* **2004**, 475–482. (b) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571–1587. (c) Suzuki, N.; Yasaki, S.; Yasuhara, A.; Sakamoto, T. *Chem. Pharm. Bull.* **2003**, *51*, 1170–1173. (d) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002**, *42*, 7699–7702. (e) Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett.* **2001**, *41*, 5275–5278. (f) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529–534. (g) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507–6511.
15. Kinderman, S. S.; de Gelder, R.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Am. Chem. Soc.* **2004**, *126*, 4100–4101.
16. Wolf, L. B.; Tjen, K. C. M. F.; Brink, H. T.; Blaauw, R. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 70–83.
17. (a) Abbiati, G.; Beccalli, E. M.; Broggini, G.; Zoni, C. *J. Org. Chem.* **2003**, *68*, 7625–7628. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 4206–4207. (c) Casalnuovo, A. L.; Calabres, J. C.; Milstein, D. *Inorg. Chem.* **1987**, *26*, 971–972. (d) Fryzuk, M. D.; Montgomery, C. D. *Coord. Chem. Rev.* **1989**, *95*, 1–40.
18. (a) Arcadi, A.; Anacardio, R.; D'Anniballe, G.; Gentile, M. *Synlett* **1997**, 1315–1317. (b) Arcadi, A. *Synlett* **1997**, 941–943.
19. Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610–618.
20. (a) Abbiati, G.; Arcadi, A.; Canevari, V.; Capezzuto, A.; Rossi, E. *J. Org. Chem.* **2005**, *70*, 6454–6460. (b) Asao, N.; Nogami, T.; Takanashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765.
21. (a) Bouyssi, D.; Cavicchioli, M.; Balme, G. *Synlett* **1997**, 944–946. (b) Monteiro, N.; Gore, J.; Balme, G. *Tetrahedron* **1992**, *48*, 10103–10114.
22. Arcadi, A.; Cacchi, S.; Marinelli, M. *Tetrahedron* **1993**, *49*, 4955–4964.
23. Kamigata, N.; Matsuhisa, A.; Taka, H.; Shimizu, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 821–827.