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Synthesis of new 3-arylindole-2-carboxylates using β,β-diaryldehydroamino acids as building blocks. Fluorescence studies

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Abstract—Several new methyl 3-arylindole-2-carboxylates were synthesized in high yields using a metal assisted [$Pd(OAc)_2$/$Cu(OAc)_2$, DMF, 130 °C] intramolecular C–N cyclization of β,β-diaryldehydroamino acids, developed by us, thus extending the scope of this reaction. The latter were obtained by a bis-Suzuki coupling of a β,β-dibromodehydroalanine with arylboronic acids bearing either electron-donating groups (EDGs) or electron-withdrawing groups (EWGs). We were able to establish general conditions for this coupling reaction [$PdCl_2$dppf·CH_2Cl_2 1:1 (20 mol %), boronic acid (5 equiv), Cs_2CO_3 (1.4 equiv), THF/H_2O 1:1, 80 °C]. This strategy constitutes a novel, general and unprecedented approach to the synthesis of 3-arylindole-2-carboxylates. The fluorescence of the differently substituted indoles prepared was studied in several polar and non-polar solvents. In general the new indoles exhibit a solvent sensitive emission. The indoles with EDGs (OCH_3 and SCH_3) have reasonable fluorescence quantum yields in all solvents except in water. The indole with the cyano groups shows high fluorescent quantum yields in all solvents studied, despite the lower solvent sensitivity of its emission. The indole with the acetyl groups only exhibits reasonable fluorescence quantum yields in protic solvents. These studies show that the new 3-arylindole-2-carboxylates are good candidates to be used as fluorescent probes.

1. Introduction

The substituted indole nucleus is found in numerous natural products, being very important in medicinal chemistry and its synthesis continues to attract much interest.

A variety of well-established classical methods for the synthesis and functionalization of indoles are now available. The accessibility of the starting materials and their compatibility with the reaction conditions generally dictate the method of choice for synthesizing a target indole. More recently palladium-catalyzed reactions have been used to synthesize indole derivatives since they are generally tolerant to a wide range of functionalities.[1] Some of these reactions are based on an intramolecular C–N cyclization of *o*-allylanilines,[2] *o*-alkynylanilines,[3–5] or dehydrophenylalanine derivatives bearing an iodine atom in the phenyl ring.[6,7]

There are only a few reports available for the synthesis of 3-arylindole-2-carboxylates. Nakamura and Ukita synthesized ethyl 3-arylindole-2-carboxylates from α-diazophosponates and 2-aminobenzophenones using a rhodium catalyst and DBU in a two step or in a one-pot procedure.[8] Recently, Takamura et al. prepared 3-substituted indole-2-carboxylates using Fisher indole synthesis of arylhydrazones obtained from α-diazoesters and aryllithium reagents.[9]

In our laboratories, we have developed a metal assisted (palladium/copper) intramolecular C–N cyclization reaction of β,β-bis(benzo[*b*]thienyl)dehydroalanines or β-(benzo[*b*]-thienyl)dehydrophenylalanines, also prepared by us, to thienoindoles, benzo[*b*]thienopyrroles or 3-(benzo[*b*]thienyl)-indoles.[10,11]

Here we describe general conditions for the synthesis of β,β-diaryldehydroamino acids in high yields by a bis-Suzuki cross-coupling of a β,β-dibromodehydroalanine[10a] with several boronic acids bearing either electron-withdrawing groups (EWGs) or electron-donating groups (EDGs). The coupling products were submitted to our intramolecular C–N cyclization conditions, giving new 3-arylindole-2-carboxylates in excellent yields, thus extending the scope of this reaction.

Keywords: β,β-Diaryldehydroamino acids; Bis-Suzuki coupling; Metal assisted C–N cyclization; 3-Arylindole-2-carboxylates; Fluorescent probes.
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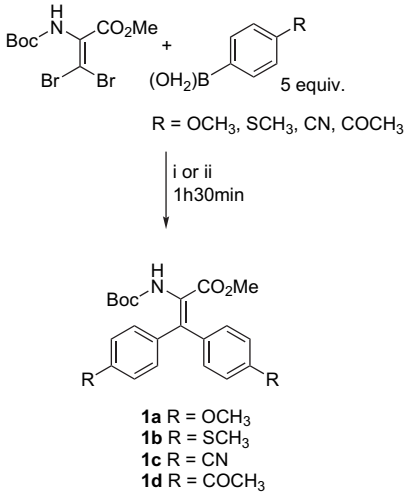
The fluorescence properties of indoles have been widely studied, mainly due to the biological relevance of these compounds and also to the utility of the indole chromophore as an intrinsic probe of the structure and function of proteins and enzymes.[12] In this work, the fluorescence properties of the synthesized new indoles were studied in several polar and non-polar solvents, showing that they may be used as solvatochromic fluorescent probes. This type of probes has found extensive applications, namely as probes for proteins,[13–15] micelles and microemulsions[16–20] and lipid membranes.[21–23] Owing to their solvent sensitive emission, the 3-arylindole-2-carboxylates prepared may be useful to probe microenvironment changes in biological media.

2. Results and discussion

2.1. Synthesis

Several β,β-diaryldehydroalanines **1a–d** were synthesized by Suzuki coupling[24] of a β,β-dibromodehydroalanine, previously prepared by us,[10a] with differently substituted phenylboronic acids (Scheme 1). Applying the conditions used earlier by us in the synthesis of β,β-bis(benzo[*b*]thienyl)dehydroalanines[10b] (Scheme 1, Conditions i) some of the coupling products were only obtained in low to moderate yields (Table 1). By changing the conditions (Scheme 1, Conditions ii) it was possible to obtain all the coupling products **1a–d** in good to high yields (Table 1), thus establishing general conditions for this bis-Suzuki coupling.



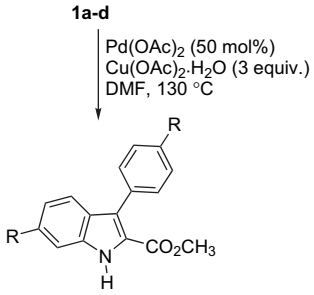
Scheme 1. (i) $PdCl_2(PPh_3)_2$ (20 mol %), Na_2CO_3 (4 equiv), DME/H_2O (10:1), 90 °C and (ii) $PdCl_2dppf{\cdot}CH_2Cl_2$ 1:1 (20 mol %), Cs_2CO_3 (1.4 equiv), THF/H_2O(1:1), 80 °C.

Table 1. Results obtained in the synthesis of β,β-diaryldehydroalanines

Compound	Yields/%	
	Conditions i	Conditions ii
1a	80	85
1b	34	74
1c	15	90
1d	41	75

In all cases, small amounts of the corresponding C–C dimers of the boronic acids and *p*-hydroxylated compounds were also isolated.

The β,β-diaryldehydroalanines **1a–d** were used as building blocks for the synthesis of new 3-arylindole-2-carboxylates **2a–d** using our metal assisted C–N intramolecular cyclization in high yields (Scheme 2). We have already studied the best reaction conditions in terms of amounts of $Pd(OAc)_2$[10b] and reaction temperature and we have proposed a mechanism involving the formation of a palladacycle followed by extrusion of Pd(0), which may be reoxidized to Pd(II) by $Cu(OAc)_2$. The cleavage of the *tert*-butoxycarbonyl group (Boc) follows the cyclization and is probably due to the acetic acid formed.[11]



Scheme 2. Synthesis of methyl 3-arylindole-2-carboxylates by a C–N intramolecular metal assisted cyclization.

The results show that the cyclization is not highly affected by the presence of EDGs or EWGs in the phenyl rings, despite the almost quantitative yields obtained for indoles **2a** and **2b**. Thus we have established a new and effective method for the synthesis of 3-arylindole-2-carboxylates from β,β-diaryldehydroamino acids as building blocks.

2.2. Fluorescence studies

The absorption and the fluorescence properties of indoles **2a–d** were studied in several solvents (Table 2). As an example, the absorption and emission spectra of compounds **2a–d** in dichloromethane are displayed in Figure 1.

The absorption maxima wavelengths of **2a–d** in several solvents are shown in Table 2. The molar extinction coefficients, ε, at λ_{max} are typical of $\pi \rightarrow \pi^*$ transitions, varying in the range $1.1\times10^4-3\times10^4\ M^{-1}\ cm^{-1}$ (Table 2). As these compounds have a heterocyclic nitrogen atom, transitions involving the non-bonding nitrogen electrons have similar properties to those of $\pi \rightarrow \pi^*$ transitions,[25,26] as the n orbital generally overlaps the π orbital of adjacent carbon atoms. In fact, the near-ultraviolet absorption of indole and their derivatives is generally attributed to two strongly overlapping $\pi \rightarrow \pi^*$ transitions,[27–29] with an average ε value for unsubstituted indole of $5550\ M^{-1}\ cm^{-1}$,[25] which also justifies its relatively high fluorescence quantum yield.[30]

All the indole derivatives prepared have a carboxylate group and it is known that many carbonyl compounds exhibit low

Table 2. Absorption and fluorescence maxima wavelengths (λ_{abs} and λ_{em}), molar extinction coefficients (ε) at absorption maximum and fluorescence quantum yields (Φ_F), relative to 9,10-diphenylanthracene in ethanol

Compound	*cyclo-C_6H_{12}*			*$C_6H_5CH_3$*			*CH_2Cl_2*			*$HCON(CH_3)_2$*		
	λ_{abs}/nm (ε/M^{-1} cm^{-1})	λ_{em}/nm	Φ_F	λ_{abs}/nm (ε/M^{-1} cm^{-1})	λ_{em}/nm	Φ_F	λ_{abs}/nm (ε/M^{-1} cm^{-1})	λ_{em}/nm	Φ_F	λ_{abs}/nm (ε/M^{-1} cm^{-1})	λ_{em}/nm	Φ_F
2a R=OCH_3	321 (2.08×10^4)	386	0.59	323 (1.84×10^4)	392	0.57	322 (1.80×10^4)	400	0.58	323 (1.80×10^4)	404	0.45
2b R=SCH_3	326 (2.33×10^4)	395	0.41	332 (1.93×10^4)	407	0.39	328 (1.90×10^4)	416	0.46	331 (1.84×10^4)	422	0.34
2c R=CN	280 (1.86×10^4), 301(sh), 332(sh)	382	0.47	307[a] (1.79×10^4), 337(sh)	391	0.38	284 (1.85×10^4), 304(sh), 335(sh)	390	0.38	287 (1.82×10^4), 305(sh), 337(sh)	398	0.41
2d R=$COCH_3$	293 (2.05×10^4), (sh)	—	≤0.001	299 (1.92×10^4), (sh)	—	≤0.001	291 (2.11×10^4), (sh)	420	0.008	298 (3.01×10^4), (sh)	423	0.03

Compound	*CH_3CN*			*CH_3CH_2OH*			*CH_3OH*			*H_2O*		
	λ_{abs}/nm (ε/M^{-1} cm^{-1})	λ_{em}/nm	Φ_F	λ_{abs}/nm (ε/M^{-1} cm^{-1})	λ_{em}/nm	Φ_F	λ_{abs}/nm (ε/M^{-1} cm^{-1})	λ_{em}/nm	Φ_F	λ_{abs}/nm (ε/M^{-1} cm^{-1})	λ_{em}/nm	Φ_F
2a R=OCH_3	320 (1.45×10^4)	401	0.50	321 (1.57×10^4)	418	0.06	321 (1.67×10^4)	422	0.03	322 (1.33×10^4)	434	0.01
2b R=SCH_3	328 (1.58×10^4)	420	0.38	329 (1.65×10^4)	430	0.28	330 (1.62×10^4)	437	0.27	329 (1.32×10^4)	443	0.05
2c R=CN	285 (1.55×10^4), 304(sh), 336(sh)	393	0.44	286 (1.30×10^4), 304(sh), 335(sh)	396	0.46	285 (1.20×10^4), 303(sh), 334(sh)	397	0.46	284 (1.10×10^4), 302(sh), 333(sh)	406	0.20
2d R=$COCH_3$	296 (2.72×10^4), (sh)	425	0.02	300 (2.73×10^4), (sh)	450	0.22	298 (2.74×10^4), (sh)	465	0.26	299 (1.81×10^4), (sh)	486	0.05

Notes: sh: shoulder.
[a] Toluene cut-off: 285 nm.

fluorescence quantum yields due to the low-lying n→π* state. Therefore, in these new indoles the electronic transitions π→π* and n→π* can be nearby in energy, resulting in state-mixing.[31] A predominance of n→π* character could explain the very weak fluorescence of compound **2d** in dichloromethane (inset of Fig. 1) and in other non-polar solvents (Table 2), as this compound bears three carbonyl groups.

In order to study the solvent sensitivity of the indoles emission, fluorescence spectra were measured in several polar and non-polar media (Figs. 2–5). The maxima emission wavelengths (λ_{em}) and fluorescence quantum yields (Φ_F) are presented in Table 2. Indoles **2a** and **2b** display significant red shifts, band enlargement and a decrease tendency in Φ_F with the increase of solvent polarity (Figs. 2 and 3, Table 2). This behaviour is typical of an intramolecular charge transfer (ICT) character of the excited state. Compound **2a** exhibits higher fluorescence quantum yields in non-protic solvents than compound **2b** probably due to the increase of singlet→triplet (S→T) intersystem crossing (ISC) by enhancement of spin-orbit coupling interaction that is usually observed in sulfur containing compounds.[31,32]

The decrease in Φ_F values with increasing hydrogen bonding capability of protic solvents (Φ_F in ethanol>Φ_F in methanol>Φ_F in water) may be due to an increase of S→T ISC efficiency through H-bond formation between fluorophores **2a** and **2b** with solvent. This behaviour is known for several compounds containing nitrogen and oxygen atoms, like 4-aminophthalimide[33] and oxazines.[34] All the indoles studied have the ability to establish hydrogen bonds with solvent,

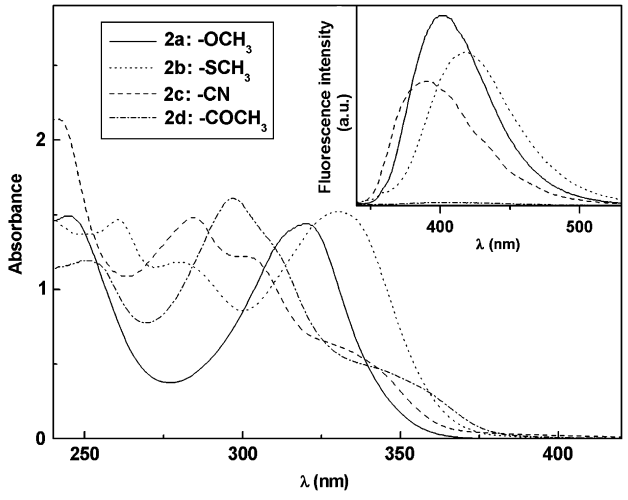


Figure 1. Absorption spectra of 8×10^{-5} M solutions of indoles **2a–d** in dichloromethane. Inset: fluorescence spectra of 2×10^{-6} M solutions of indoles **2a–d** in dichloromethane (λ_{exc}=325 nm).

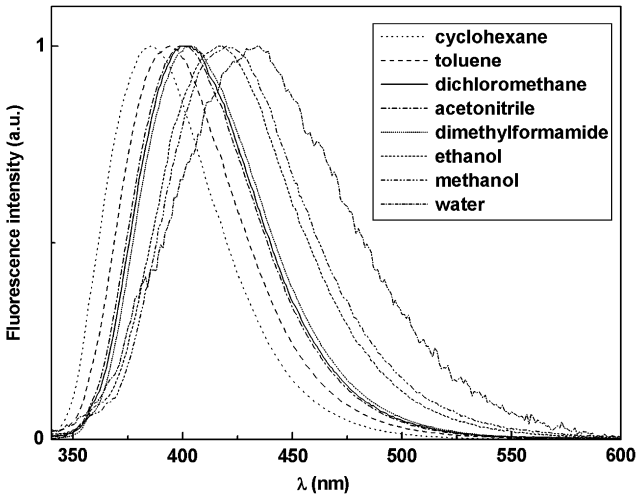


Figure 2. Normalized fluorescence spectra of indole **2a** (R=OCH_3) in different solvents (λ_{exc}=325 nm).

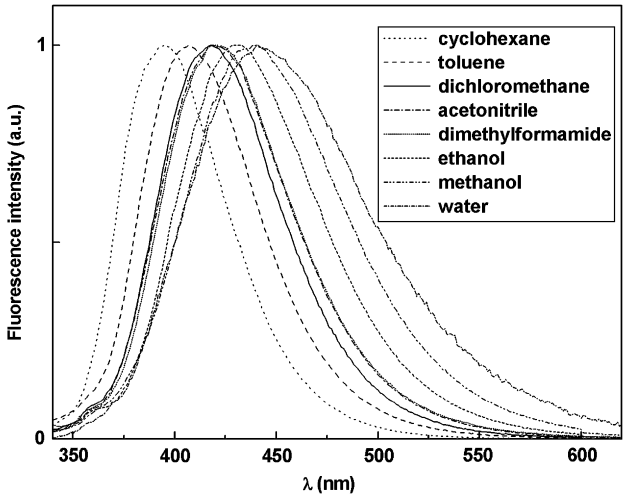


Figure 3. Normalized fluorescence spectra of compound **2b** (R=SCH_3) in different solvents (λ_{exc}=325 nm).

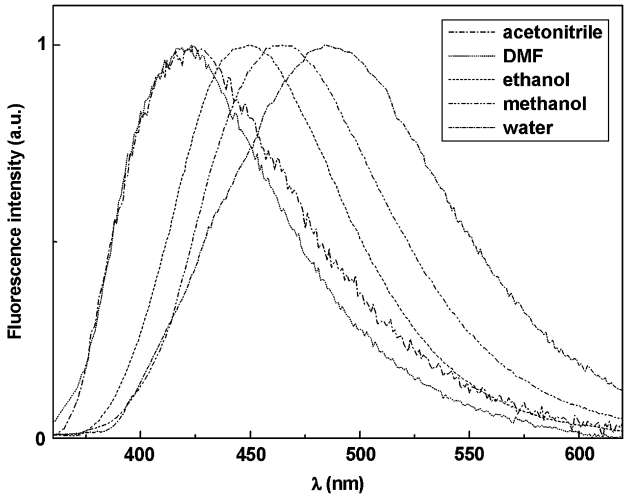


Figure 5. Normalized fluorescence spectra of compound **2d** (R=$COCH_3$) in different solvents (in the other solvents, compound **2d** is not fluorescent).

through the donating properties of the indole N–H and accepting properties of the carboxylate group. In protic solvents Φ_F values for compound **2b** are higher than those for **2a** due the lower acceptor H-bonding character of the sulfur atom compared with the oxygen atom.

Due to the strong dependence of **2a** and **2b** fluorescence with solvent polarity, these compounds are considered good fluorescent probes. Also, the four compounds **2a–d** can be excited at wavelengths longer than 320 nm (Table 2), allowing the investigation of microenvironment changes when incorporated in peptides and proteins, without simultaneous excitation of tryptophan and other fluorescent amino acids (tyrosine and phenylalanine), which absorb light at λ <300 nm.[25,32] The fluorescence resonance energy transfer (FRET) from amino acids to the fluorophores is also avoided with excitation at λ >320 nm.

The emission spectra for compound **2c** (Fig. 4) show small red shifts with increasing solvent polarity, except in water. Lower variations in fluorescence quantum yields are observed when compared with those of **2a** and **2b** (Table 2), which points to a lower ICT interaction. In water, the formation of solute–solvent hydrogen bonds may explain the significant red shift in emission and the decrease in Φ_F value.

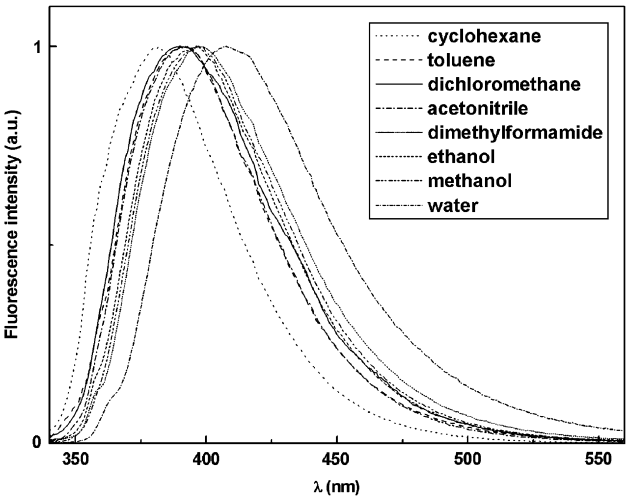


Figure 4. Normalized fluorescence spectra of compound **2c** (R=CN) in different solvents (λ_{exc}=325 nm).

Although compound **2c** shows to be less sensitive to the environment than compounds **2a** and **2b**, it maintains a reasonable fluorescence quantum yield in all solvents, including water. This makes indole **2c** useful as probe for water-rich environments in biological systems and for controlled drug release assays, allowing quenching studies of its fluorescence.

Compound **2d** (Fig. 5) only exhibits fluorescence in polar media, its fluorescence quantum yield rises with increasing solvent polarity, except in water. A strong dependence of Φ_F values with solvent polarity, as observed for **2d**, can be explained by the existence of a low-lying $\pi\rightarrow\pi^*$ state but with a $n\rightarrow\pi^*$ only slightly higher in energy. In non-polar solvents, the $n\rightarrow\pi^*$ state energy can be lower than that of $\pi\rightarrow\pi^*$ state, giving low Φ_F values. With increasing solvent polarity and/or hydrogen bonding capability, $\pi\rightarrow\pi^*$ state can shift to lower energy than $n\rightarrow\pi^*$ and the fluorescence quantum yield rises. The increase of $S\rightarrow T$ intersystem crossing efficiency through H-bond formation between **2d** and water may explain the lower Φ_F value when compared to those in alcohols.

Solvatochromic shifts caused by general (not specific) solvent effects are often described by the Lippert–Mataga Eq. 1, which relates the energy difference between absorption and emission maxima to the orientation polarizability,[32,35]

$$\overline{\nu}_{abs} - \overline{\nu}_{fl} = \frac{1}{4\pi\varepsilon_0}\frac{2\Delta\mu^2}{hcR^3}\Delta f + \text{const} \quad (1)$$

where $\overline{\nu}_{abs}$ is the wave number of maximum absorption, $\overline{\nu}_{fl}$ is the wave number of maximum emission, $\Delta\mu=\mu_e-\mu_g$ is the difference in the dipole moment of solute molecule between excited (μ_e) and ground (μ_g) states, R is the cavity radius (considering the fluorophore a point dipole at the centre of

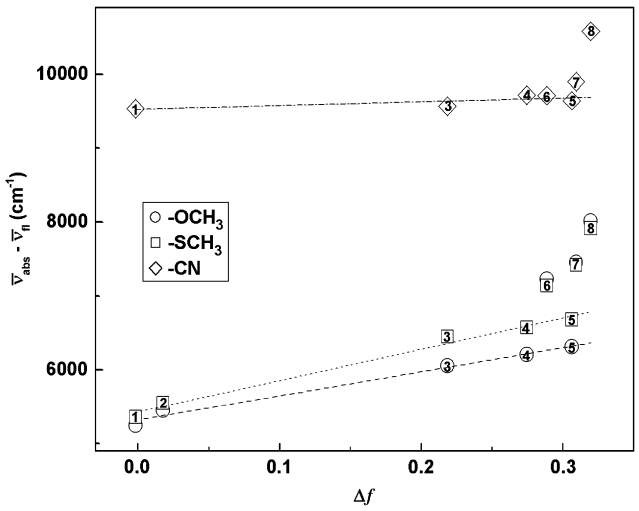


Figure 6. Lippert–Mataga plot for compounds **2a–c**. 1: cyclohexane; 2: toluene; 3: dichloromethane; 4: *N*,*N*-dimethylformamide; 5: acetonitrile; 6: ethanol; 7: methanol; 8: water (values of ε and n were obtained from Ref. 36).

a spherical cavity immersed in the homogeneous solvent), and Δf is the orientation polarizability given by Eq. 2:

$$\Delta f = \frac{\varepsilon - 1}{2\varepsilon + 1} - \frac{n^2 - 1}{2n^2 + 1} \quad (2)$$

where ε is the static dielectric constant and n the refractive index of the solvent.

The Lippert–Mataga plots for compounds **2a–c** are shown in Figure 6. The plots are reasonably linear in non-protic solvents. Positive deviations are observed in protic solvents, confirming specific solute–solvent interactions by hydrogen bonds. This justifies the larger deviations observed for compound **2a** (R=OCH$_3$).

From ab initio molecular quantum chemistry calculations, the cavity radius and ground state dipole moment were determined, through an optimized structure provided by GAMESS software[37] (Table 3). These values allow the estimation of excited state dipole moments from the Lippert–Mataga plots (Table 3).

The μ_e values for compounds **2a** and **2b** are typical of planar ICT states. Twisted intramolecular charge transfer (TICT) states are usually present in secondary aromatic amines,[38] but exhibit much higher excited state dipole moments. It can be observed that the presence of two SCH$_3$ groups in compound **2b** provides a larger increase in polar character of the excited state. As predicted above, the excited state of compound **2c** has a less ICT character.

Table 3. Cavity radius (R) and ground state dipole moments (μ_g), obtained from theoretical calculations and excited state dipole moments (μ_e) calculated from Lippert–Mataga plots

Compound	Cavity radius, R/Å	Ground state dipole moment, μ_g/D	Excited state dipole moment, μ_e/D
2a R=OCH$_3$	5.5	2.31	9.68
2b R=SCH$_3$	6.3	2.47	12.7
2c R=CN	5.2	4.51	7.2

3. Conclusions

We have developed a new and versatile strategy for the synthesis in high yields of fluorescent 3-arylindole-2-carboxylates using palladium-catalyzed/assisted reactions: a bis-Suzuki coupling and a Pd/Cu intramolecular C–N cyclization reaction of β,β-diaryldehydroamino acids. The latter were prepared in high yields from a β,β-dibromodehydroalanine derivative and several arylboronic acids bearing EWGs or EDGs, and we were able to establish general conditions for this reaction.

The fluorescence properties of indoles bearing EDGs (OCH$_3$ and SCH$_3$) show that they can be used as fluorescent probes, due to the solvent sensitivity of their emission. Thus, they are adequate for monitoring changes in microenvironment in biological systems, especially indole bearing SCH$_3$ groups, as it shows reasonable fluorescence quantum yields in both protic and non-protic solvents. The indole with cyano groups may be useful when incorporated in water-rich environments, while the indole with acetyl groups can be used to report changes in media with hydrogen bonding capability. Therefore, the synthetic strategy presented is very useful to obtain differently substituted 3-arylindole-2-carboxylates that can be employed as fluorescent probes with different environment sensitivities and reasonable quantum yields in almost all kind of solvents.

4. Experimental section

4.1. Synthesis

4.1.1. General considerations. Melting points (°C) were determined in a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus at 300 and 75.4 MHz, respectively. ^{1}H–^{1}H spin–spin decoupling and DEPT θ 45° as a differential techniques in the ^{13}C NMR spectra, were used. HMQC and HMBC experiments were used. MS (EI) and HRMS data were recorded by the mass spectrometry service of the University of Vigo, Spain. Elemental analysis was performed on a LECO CHNS 932 elemental analyser.

The reactions were monitored by thin layer chromatography (TLC). Column chromatography was performed on Macherey-Nagel silica gel 230–400 mesh. Petroleum ether refers to the boiling range 40–60 °C. When solvent gradient was used, the increase of polarity was made from neat petroleum ether to mixtures of ether/petroleum ether, increasing 10% of ether each time until the isolation of the product.

4.1.2. General procedures for the synthesis of compounds 1a–d. *Procedure A*: To a solution of Boc–ΔAla(β,β-Br)–OMe[10a] (0.100 mmol, 36.0 mg) in DME/H$_2$O (10:1), the boronic acid (5 equiv), Na$_2$CO$_3$ (4 equiv) and PdCl$_2$(PPh$_3$)$_2$ (20 mol %) were added. The reaction was heated for 1 h 30 min, at 90 °C. The DME was removed under reduced pressure and the residue taken from ethyl acetate (15 mL). The organic layer was washed with water and brine (2×5 mL) and dried with MgSO$_4$. After removal of the solvent the residue was submitted to column chromatography.

Procedure B: The same procedure described above was used changing Na_2CO_3 (4 equiv) by Cs_2CO_3 (1.4 equiv), $PdCl_2(PPh_3)_2$ by Pd(dppf)Cl_2·DCM (1:1) and DME/H_2O (10:1) by THF/H_2O (1:1) (Scheme 1).

4.1.2.1. Boc–ΔAla[β,β-bis(4-methoxyphenyl)]–OMe (1a). Using general procedure A, (4-methoxy)phenylboronic acid (0.500 mmol, 76.0 mg). Column chromatography using solvent gradient from neat petroleum ether to 40% diethyl ether in petroleum ether gave compound **1a** (42.0 mg, 80%) as a yellow solid; mp 158.0–159.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.46 (s, 9H, CH_3 Boc), 3.57 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.02 (br s, 1H, NH), 6.82 (d, J=9.0 Hz, 2H, ArH), 6.89 (d, J=9.0 Hz, 2H, ArH), 7.04 (d, J=9.0 Hz, 2H, ArH), 7.16 (d, J=9.0 Hz, 2H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 28.17 ($C(CH_3)_3$), 51.97 (OCH_3), 55.18 (OCH_3), 55.28 (OCH_3), 81.04 ($OC(CH_3)_3$), 113.49 (2CH), 114.03 (2CH), 124.02 (C), 130.50 (2CH), 131.04 (C), 131.40 (2CH), 132.46 (C), 134.29 (C), 153.06 (C=O), 159.35 (C), 159.51 (C), 167.06 (C=O) ppm. Elemental analysis calcd (%) for $C_{23}H_{27}NO_6$ (413.47) C 66.81, H 6.58, N 3.39; found C 66.39, H 6.74, N 3.74.

Using procedure B compound **1a** was obtained in 85% yield.

4.1.2.2. Boc–ΔAla{β,β-bis[4-methylsulfanyl(phenyl)]}–OMe (1b). Using procedure A, acid 4-methylthiophenylboronic (0.500 mmol, 84.0 mg). Column chromatography using solvent gradient from petroleum ether to 40% diethyl ether in petroleum ether gave compound **1b** (15.0 mg, 34%) as an oil. Crystallization from diethyl ether/petroleum ether gave a light yellow solid; mp 135.0–136.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.46 (s, 9H, CH_3 Boc), 2.48 (s, 3H, SCH_3), 2.51 (s, 3H, SCH_3), 3.58 (s, 3H, OCH_3), 6.04 (br s, 1H, NH), 7.03 (d, J=8.7 Hz, 2H, ArH), 7.13–7.16 (m, 4H, ArH), 7.23 (d, J=8.4 Hz, 2H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=15.22 (SCH_3), 15.37 (SCH_3), 28.14 ($C(CH_3)_3$), 52.07 (OCH_3), 81.30 ($OC(CH_3)_3$), 125.20 (C), 125.71 (2CH), 126.07 (2CH), 129.62 (2CH), 130.37 (2CH), 133.01 (C), 134.92 (C), 136.27 (C), 138.60 (C), 139.35 (C), 152.80 (C=O), 166.58 (C=O) ppm. Elemental analysis calcd (%) for $C_{23}H_{27}NO_4S_2$ (445.59) C 62.00, H 6.11, N 3.14, S 14.39; found C 62.06, H 6.22, N 3.21, S 14.45.

Using procedure B the yield for compound **1b** was increased to 74% yield.

4.1.2.3. Boc–ΔAla[β,β-bis-(4-cyanophenyl)]–OMe (1c). Using procedure B, acid 4-cyanophenylboronic (0.500 mmol, 74.0 mg). Column chromatography using solvent gradient from petroleum ether to 60% diethyl ether in petroleum ether gave compound **1c** (36.0 mg, 90%) as a white solid; mp 187.0–188.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.44 (s, 9H, CH_3 Boc), 3.59 (s, 3H, OCH_3), 6.11 (br s, 1H, NH), 7.22 (d, J=8.4 Hz, 2H, ArH), 7.34 (d, J=8.4 Hz, 2H, ArH), 7.61 (d, J=8.4 Hz, 2H, ArH), 7.69 (d, J=8.4 Hz, 2H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=28.02 ($C(CH_3)_3$), 52.48 (OCH_3), 82.36 ($OC(CH_3)_3$), 112.07 (C), 112.47 (C), 118.09 (C), 118.31 (C), 128.62 (C), 129.88 (2CH), 130.49 (2CH), 131.19 (C), 132.16 (2CH), 132.79 (2CH), 142.51 (C), 143.56 (C), 152.01 (C=O), 165.08 (C=O) ppm. Elemental analysis calcd (%) $C_{23}H_{21}N_3O_4$ (403.44) C 68.47, H 5.25, N 10.42; found C 68.19, H 5.29, N 10.28.

Using procedure A compound **1c** was only obtained in 15% yield.

4.1.2.4. Boc–ΔAla[β,β-bis(4-acetylphenyl)]–OMe (1d). Using general procedure A, acid 4-acetylphenylboronic (0.500 mmol, 82.0 mg). Column chromatography using solvent gradient from pure petroleum ether to 60% diethyl ether in petroleum ether gave compound **1d** (18.0 mg, 41%) as a white solid; mp 129.0–129.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.46 (s, 9H, CH_3 Boc), 2.60 (s, 3H, $COCH_3$), 2.62 (s, 3H, $COCH_3$), 3.59 (s, 3H, OCH_3), 6.09 (br s, 1H, NH), 7.22 (d, J=8.4 Hz, 2H, ArH), 7.33 (d, J=8.4 Hz, 2H, ArH), 7.90 (d, J=8.4 Hz, 2H, ArH), 7.98 (d, J=8.4 Hz, 2H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=26.57 (CH_3), 26.60 (CH_3), 28.06 ($C(CH_3)_3$), 52.29 (OCH_3), 81.95 ($OC(CH_3)_3$), 127.69 (C), 128.28 (2CH), 128.86 (2CH), 129.38 (2CH), 130.07 (2CH), 130.08 (C), 136.39 (C), 136.77 (C), 142.81 (C), 143.99 (C), 152.37 (C=O), 165.65 (C=O), 197.29 (C=O), 197.42 (C=O) ppm. Elemental analysis calcd (%) for $C_{25}H_{27}NO_6$ (437.49) C 68.64, H 6.22, N 3.20; found C 68.65, H 6.38, N 3.25.

Using procedure B the yield for compound **1d** was increased to 75%.

4.1.3. General procedure for the synthesis of indoles 2a–d. To a solution of the β,β-diaryldehydroalanine derivatives **1a–d** (0.1 M) in DMF, $Pd(OAc)_2$ (50 mol %) and $Cu(OAc)_2·H_2O$ (3 equiv) were added and the reaction mixture heated at 130 °C. Ethyl acetate (50 mL) was added and the solution washed with water and brine (2×25 mL each), dried with $MgSO_4$ and the solvent evaporated at reduced pressure to give an oil.

4.1.3.1. Methyl 6-methoxy-3-(4-methoxyphenyl)-1*H*-indole-2-carboxylate (2a). Indole **2a** was prepared from compound **1a** (0.300 mmol, 125 mg) according to the general procedure described above, heating for 3 h. A dry flash of the residue using solvent gradient from 30% diethyl ether/petroleum ether to 50% diethyl ether/petroleum ether gave compound **2a** (92.0 mg, 99%) as a white solid; mp 157–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.82 (s, 3H, CO_2CH_3), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.80–6.84 (m, 2H, 5- and 7-H), 7.01 (d, J=8.7 Hz, 2H, 3′- and 5′-H), 7.49–7.53 (m, 3H, 2′-, 6′- and 4-H), 8.88 (br s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=51.58 (CO_2CH_3), 55.25 (OCH_3), 55.51 (OCH_3), 93.35 (CH), 112.24 (CH), 113.36 (3′- and 5′-CH), 120.97 (C), 122.39 (C), 122.70 (CH), 124.73 (C), 125.67 (C), 131.55 (2′- and 6′-CH), 136.81 (C), 158.86 (C), 159.27 (C), 162.36 (C=O) ppm. Elemental analysis calcd (%) for $C_{18}H_{17}NO_4$ (311.33) C 69.44, H 5.50, N 4.50; found C 69.12, H 5.64, N 4.58.

4.1.3.2. Methyl 6-methylthio-3-[4-(methylthio)-phenyl]-1*H*-indole-2-carboxylate (2b). Indole **2b** was prepared from compound **1b** (0.300 mmol, 125 mg) according to the general procedure described above, heating at 130 °C for 2 h 30 min. Compound **2b** was obtained (102 mg, 99%) as a light yellow solid; mp 136.0–137.0 °C. ^{1}H NMR

(300 MHz, acetone-d_6): δ=2.57 (s, 3H, SCH_3), 2.58 (s, 3H, SCH_3), 3.81 (s, 3H, OCH_3), 7.10 (dd, J=8.7 and 1.5 Hz, 1H, 5-H), 7.39 (d, J=8.7 Hz, 2H, 3′- and 5′-H), 7.49 (d, J=1.5 Hz, 1H, 7-H), 7.52–7.55 (m, 3H, 2′- and 6′-H and 4-H), 10.92 (br s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, acetone-d_6): δ=15.36 (SCH_3), 16.06 (SCH_3), 51.71 (OCH_3), 110.12 (CH), 121.44 (CH), 122.10 (CH), 123.12 (C), 123.87 (C), 126.15 (C) 126.38 (3′- and 5′-CH), 131.11 (C), 131.80 (2′- and 6′-CH), 136.90 (C), 137.90 (C), 138.27 (C), 162.45 (C=O) ppm. *m/z* IE (%) 343 (M^+, 100), 311 (M^+−OMe, 39), 236 (75). HMRS: Calculated for $C_{18}H_{11}NO_2S_2$ 343.0701; found [M^+] 343.0700.

4.1.3.3. Methyl 6-cyano-3-(4-cyanophenyl)-1*H*-indole-2-carboxylate (2c). Indole **2c** was prepared from compound **1c** (0.250 mmol, 112 mg) according to the general procedure described above, heating at 130 °C for 2 h 30 min. Compound **2c** was obtained (80.0 mg, 83%) as a yellow solid; mp 262.0–264.0 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ=3.87 (s, 3H, OCH_3), 7.49 (dd, J=8.4 and 0.9 Hz, 1H, 5-H), 7.80 (d, J=8.4 Hz, 1H, 4-H), 7.83 (d, J=8.1 Hz, 2H, 2′- and 6′-H), 7.93 (d, J=8.1 Hz, 2H, 3′- and 5′-H), 8.09 (s, 1H, 7-H), 11.80 (br s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, acetone-d_6): δ=52.41 (OCH_3), 108.90 (C), 111.77 (C), 118.62 (C), 118.67 (CH), 119.44 (C), 120.11 (C), 122.03 (C), 122.77 (CH), 124.05 (CH), 130.42 (C), 132.37 (2′- and 6′-CH), 132.62 (3′- and 5′-CH), 135.89 (C), 138.74 (C), 161.74 (C=O) ppm. *m/z* IE (%) 301 (M^+, 61), 269 (M^+−OMe, 100). HMRS: Calculated for $C_{18}H_{11}N_3O_2$ 301.0851; found [M^+] 301.0851.

4.1.3.4. Methyl 6-acetyl-3-(4-acetylphenyl)-1*H*-indole-2-carboxylate (2d). Indole **2d** was prepared from compound **1d** (0.300 mmol, 125 mg) according to the general procedure described above, heating at 130 °C for 2 h. Crystallization from ethyl acetate/diethyl ether gave **2d** as a light brown solid (80.0 mg, 84%); mp 176.5–178.0 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ=2.67 (s, 3H, $COCH_3$), 2.68 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 7.69 (d, J=8.4 Hz, 1H, 4-H), 7.74 (d, J=8.1 Hz, 2H, 2′- and 6′-H), 7.82 (d, J=8.4 Hz, 1H, 5-H), 8.12 (d, J=8.1 Hz, 2H, 3′- and 5′-H), 8.31 (s, 1H, 7-H), 11.50 (br s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, acetone-d_6): δ=26.70 (CH_3), 26.83 (CH_3), 52.17 (OCH_3), 114.65 (CH), 121.18 (CH), 121.47 (CH), 122.63 (C), 127.06 (C), 128.66 (3′- and 5′-CH), 130.94 (C), 131.56 (2′- and 6′-CH), 135.42 (C), 136.57 (C), 136.80 (C), 139.08 (C), 162.04 (C=O), 197.59 (C=O), 197.61 (C=O) ppm. *m/z* IE (%) 335 (M^+, 100), 304 (M^+−OMe, 18). HMRS: Calculated for $C_{20}H_{17}NO_4$ 335.1158; found [M^+] 335.1160.

4.2. Spectroscopic measurements

All solutions were prepared using spectroscopic grade solvents and Milli-Q grade water. The fluorescence quantum yields (Φ_s) were determined using the standard method (Eq. 3).[39] 9,10-Diphenylanthracene in ethanol was used as reference, Φ_r=0.95.[40]

$$\Phi_s = \left[\frac{\left(A_r F_s n_s^2\right)}{\left(A_s F_r n_r^2\right)}\right]\Phi_r \qquad (3)$$

Where A is the absorbance at the excitation wavelength, F the integrated emission area and n the refraction index of the solvents used. Subscripts refer to the reference (r) or sample (s) compound.

Absorption spectra were recorded in a Shimadzu UV-3101PC UV–vis-NIR spectrophotometer. Fluorescence measurements were performed using a Spex Fluorolog 212 spectrofluorimeter. For fluorescence quantum yield determination (λ_{exc}=325 nm), the solutions were previously bubbled for 20 min with ultra pure nitrogen. Fluorescence spectra were corrected for the instrumental response of the system.

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