

Article

Cyclization vs. Cyclization/Dimerization in *o*-Amidostilbene Radical Cation Cascade Reactions: The Amide Question

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Abstract: The *n*-butyramido, isobutyramido, benzamido, and furancarboxamido functions profoundly modulate the electronics of the stilbene olefinic and NH groups and the corresponding radical cations in ways that influence the efficiency of the cyclization due presumably to conformational and stereoelectronic factors. For example, isobutyramido-stilbene undergoes FeCl₃ promoted cyclization to produce only indoline, while *n*-butyramidostilbene, under the same conditions, produces both indoline and bisindoline.

Keywords: stilbene; indoline; bisindoline; FeCl₃

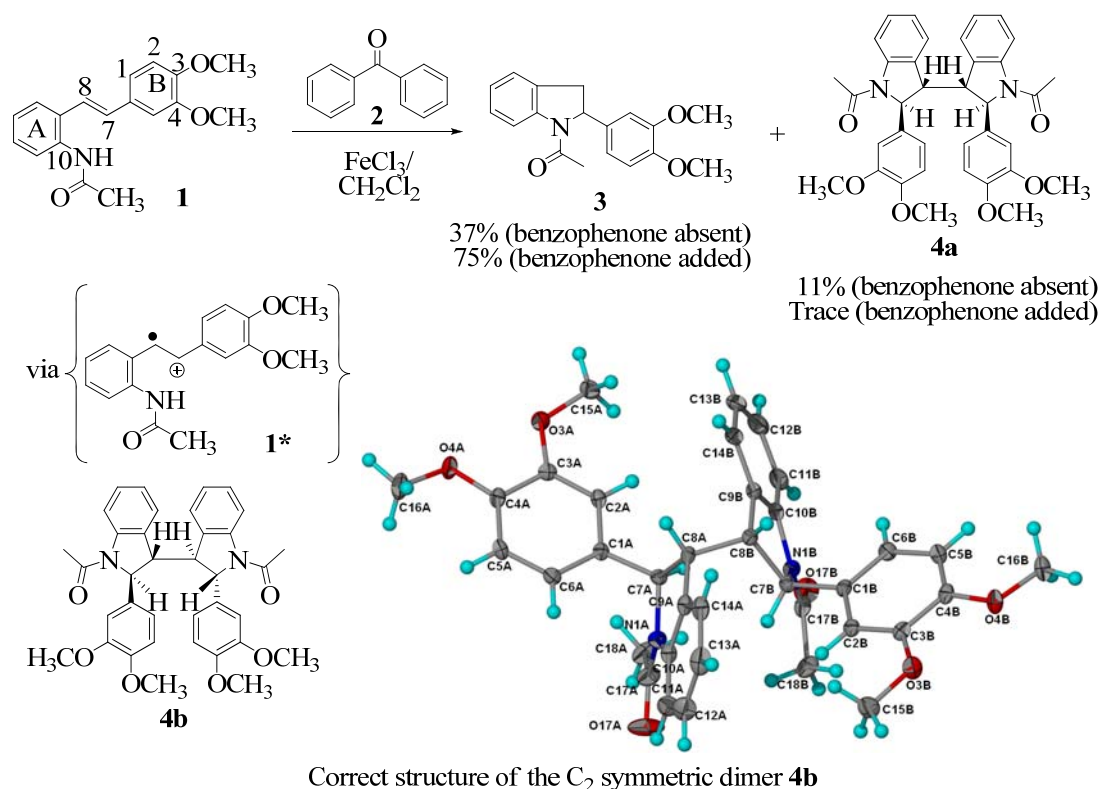
1. Introduction

A large number of biologically active compounds incorporate indole and indoline moieties, particularly those that possess C-2 phenyl or heteroaryl moieties [1]. A vast array of creative approaches to the indoline ring system have been reported recently, for example the 1,6-H transfer

followed by the 5-*exo*-trigonal ring closure tactic that exploits *o*-nitrobenzaldehyde [2]; the 5-*endo*-trigonal ring closure of *N*-(*o*-bromophenyl)ene carbamates [3]; intramolecular carbolithiation [4]; reduction of indoles [5] and the thermal reaction of *N*-allylaniline and various alkoxyamines [6]. Creative bisindoline construction is also increasing in importance as recent developments clearly indicate. For example, the highly efficient successive amide transfer approach leading to C₂ symmetric bisindolines [7]; diaza-Cope rearrangement resulting in C₃-C_{3'} bisisoindolines [8] and the [CoCl(PPh₃)₃] mediated indolyl bromide homolysis/dimerisation [9].

In 2004, we described the then unprecedented FeCl₃-promoted acetamidostilbene radical cation **1*** cascade culminating in the indoline **3** and bisindoline **4a** [10]. A subsequent X-ray analysis of the bisindoline has shown that the correct structure should be the C₂ symmetric dimer **4b** (Scheme 1) [11]. Four years later, we published the unexpected discovery that benzophenone (**2**) was capable of producing ca. a doubling of the yield of the indoline with concomitant suppression of bisindoline **4** formation (Scheme 1) [12]. The benzophenone was almost recovered always quantitatively. We proposed a Fe³⁺ benzophenone ketyl radical/stilbene radical cation catalytic cycle in that paper. Enhancement of indoline formation by an “internal agent” or via structural modification of the stilbene starting material was not envisaged.

Scheme 1. Oxidative coupling of 3,4-dimethoxy-acetamido stilbene (**1**).



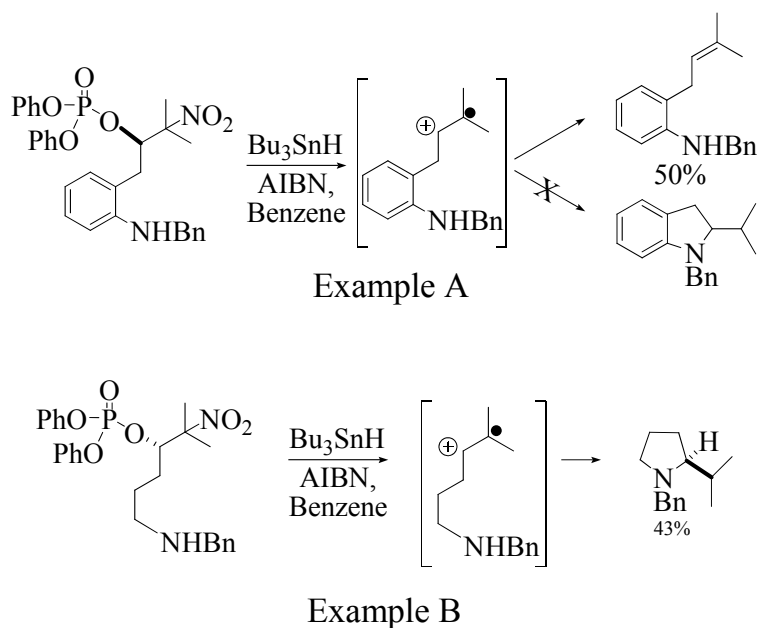
The transformation shown in Scheme 1 proceeds via the radical cation (**1***) followed by cyclization through the amidic NH to yield the indolyl radical and hence the products **3** and **4**. One question that we have not addressed is the relationship between the amide structure and the efficiency of the cyclization.

An *n*-butyramide (in place of the acetamide in Scheme 1) would be expected, on steric grounds, to engage the C(7) benzylic cation with greater difficulty than stilbene **1**. Cyclization (via FeCl₃) in the case of the isobutyramidostilbene would constitute an even greater steric impediment to indoline formation. Would the furan carboxamido and benzamido moieties undergo cyclization with comparable efficiency or are there delicate conformational factors at work here?

We reported last year full spectroscopic details of several novel stilbenes that were prepared by the Heck procedure [13]. The amido NH in stilbene **6** is more shielded than **5** (Table 1), which suggests that the amide in **6** should be somewhat more nucleophilic (under neutral or slightly acidic conditions).

On the other hand, the NMR spectra also reveal that the furancarboxamido stilbene **11** and the benzamidostilbene **7** possess even more deshielded NHs compared to stilbenes **6** and **5**. It could be argued, all other things being equal, that this significant withdrawal of electron density away from the amide NH could reduce the nucleophilicity of the amide group and thus adversely affect cyclization of the radical cation, in contrast to the cyclization of **5** or **6**. It is significant that Crich's heterocyclization of a non-oxidatively derived non-stilbene radical cation fails in the case of A but is successful in the case of B (see Scheme 2). The different cyclization outcomes for A and B appear to be due to the severely reduced nucleophilicity of the benzylaniline in A compared to B.

Scheme 2. Examples of Crich's alkene radical cation cyclizations [14].



Another interesting observation relates to the olefinic multiplets. For the furancarboxamido stilbenes **9-12**, the C(8)-H proton is more deshielded than the C(7)-H proton, the one noticeable exception being stilbene **9**, where the C(7)-H is significantly more deshielded. This might mean that exposure of stilbene **9** to FeCl₃ could produce a radical cation in which the positive charge was now at C(8) rather than C(7) (in contrast to the usual pattern). The chemical shifts discussed above may be depicted as shown in Table 1.

Table 1. $^1\text{H-NMR}$ [400MHz, δH (J, Hz)] of stilbenes 5-12 in CDCl_3 .

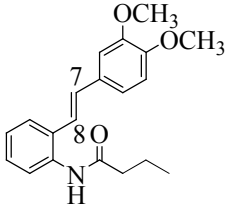
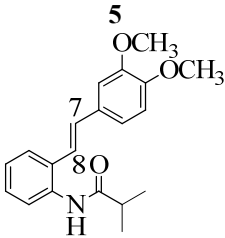
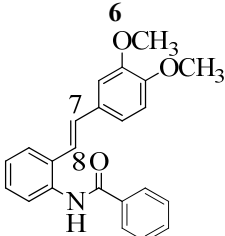
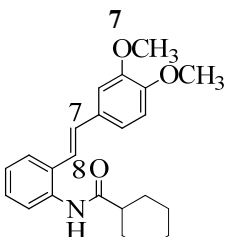
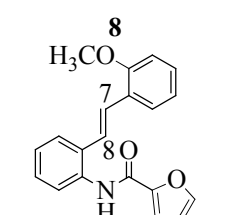
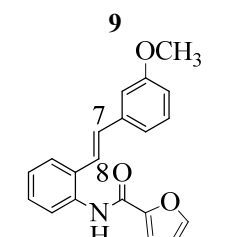
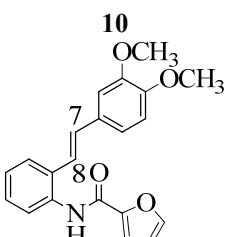
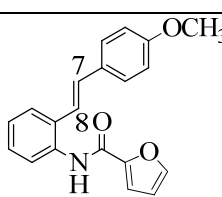
Entry	Stilbene	C(7)-H (J, Hz)	C(8)-H (J, Hz)	N-H (J, Hz)
1		6.85	6.95	7.56
2		6.90	6.97	7.31
3		6.93	7.04	8.03
4		6.91	6.97	7.21
5		7.40	7.29	8.25
6		7.02	7.22	8.17
7		6.96	7.07	8.19

Table 1. Cont.

8		7.00	7.09	8.17
	12			

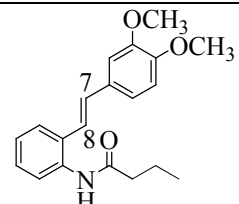
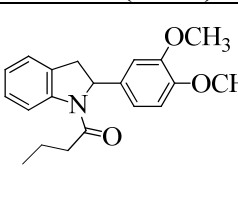
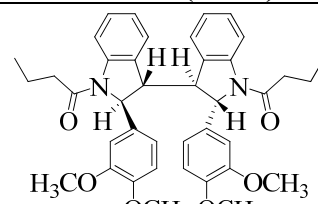
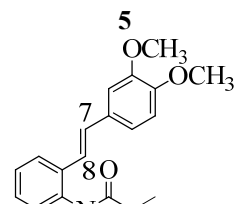
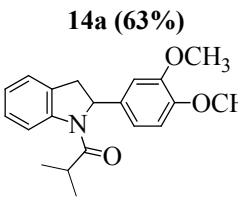
In order to unveil structural (electronic) and possible conformational influences on our radical cation cascade cyclization/dimerization, experiments were performed as described in the next section. We included stilbene **9** in our study to investigate the possibility of mesomeric stabilization by the *ortho*-methoxy substituent of the C(7) carbenium ion with the unpaired electron at C(8). Stilbene **10** was included to confirm an observation first reported in 2009 [15] where a *meta*-methoxy substituent directs radical cation formation in a way that is opposite to that observed with a *para*-methoxy substituent. We included stilbene **12** to examine the implications of having 4-methoxy substituent (rather than 3,4-dimethoxy substitution) on the formation of the radical cation.

2. Results and Discussion

2.1. FeCl₃ Promoted Syntheses of Indolines

Eight carboxamidostilbenes were constructed by the Heck protocol [13]. These stilbenes were then subjected to our FeCl₃ reaction conditions as shown below (Table 2). The resulting observations demand a more complex explanation than we had anticipated based on previous experience [10].

Table 2. FeCl₃ promoted syntheses of indolines and bisindolines.

Entry	Stilbene	Indoline (Yield)	Bisindoline (Yield)
1		 14a (63%)	 14b (6%)
2		 15 (29%)	-

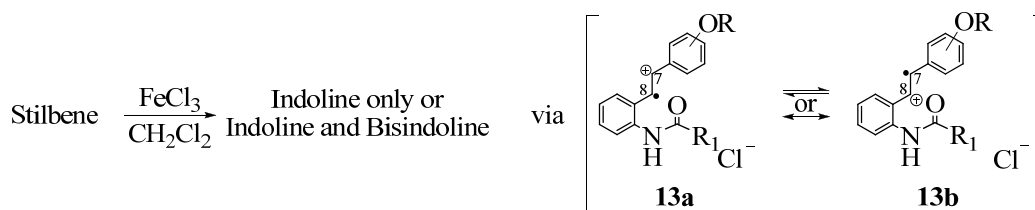
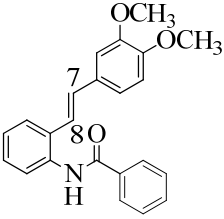
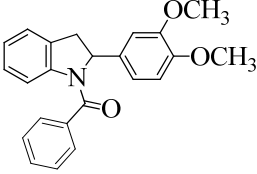
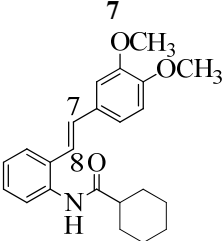
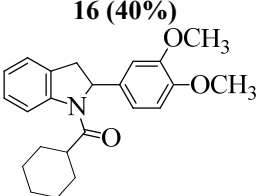
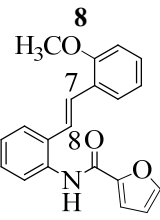
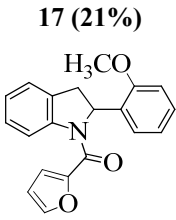
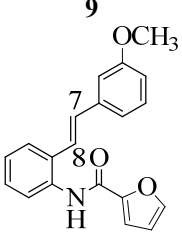
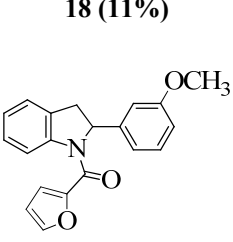
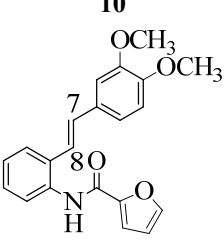
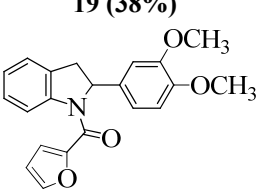
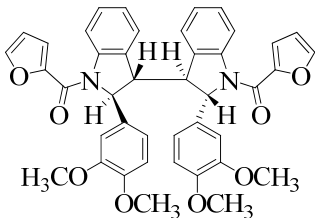
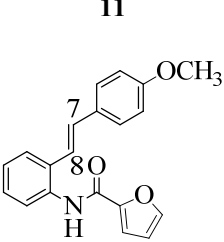
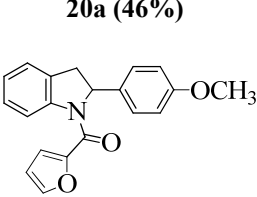
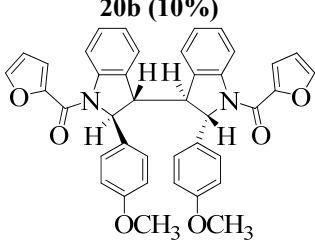


Table 2. Cont.

3			-
4		16 (40%) 	-
5		17 (21%) 	-
6		18 (11%) 	-
7		19 (38%) 	
8		20a (46%) 	20b (10%) 
	12	21a (21%)	21b (12%)

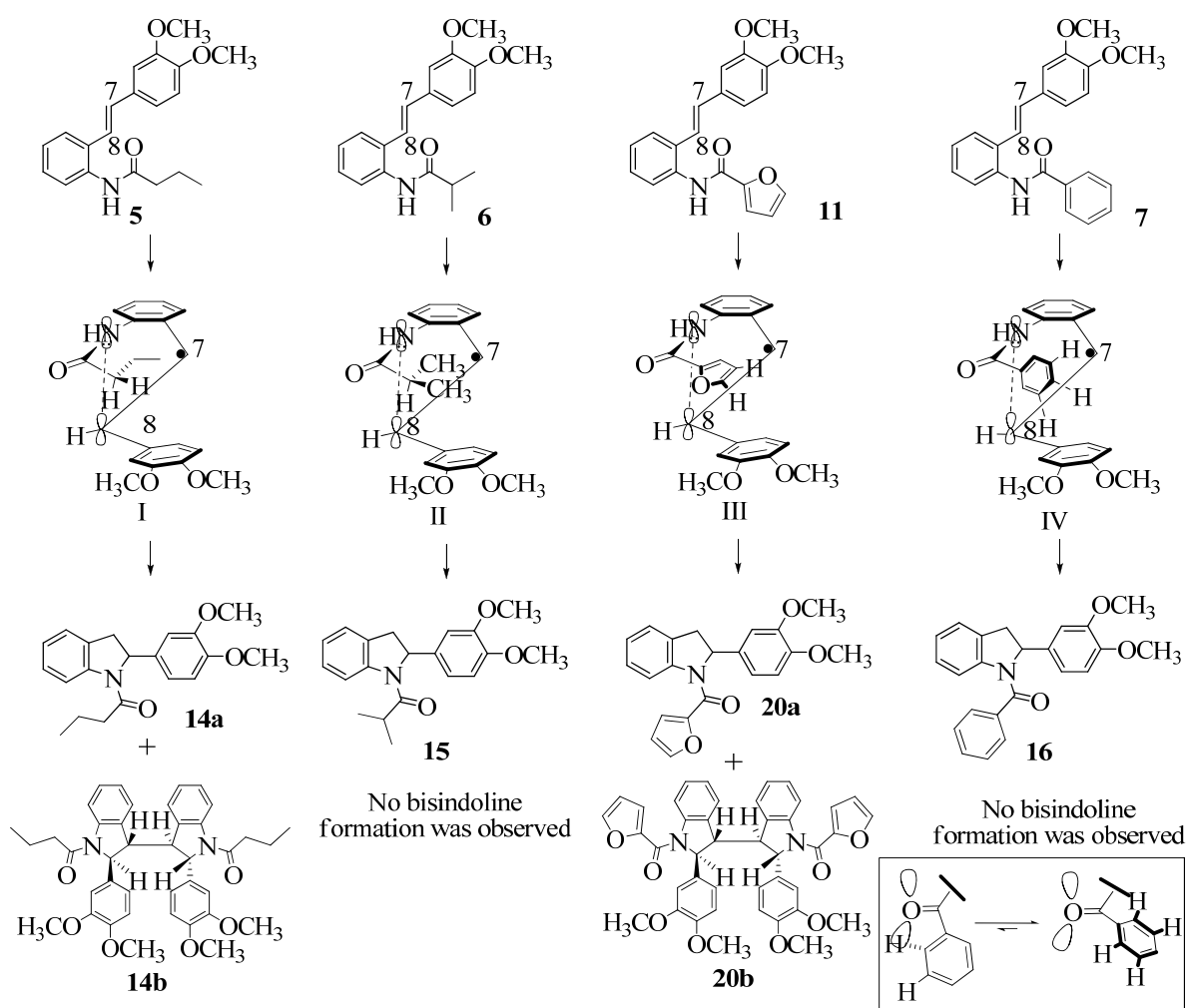
Oxidation of the stilbene **5** with FeCl_3 gave rise to indoline **14a** (63%) and bisindoline **14b** (6%) (*in the absence of benzophenone*) via radical cation **13a** (in contrast to the transformation in Scheme 1) an unexpected result. We had previously reported that the 10-acetamido-4-methoxystilbene on exposure to FeCl_3 produced the bisindoline in 24% yield and the indoline in 16% yield [15]. This “4-methoxy effect” is also seen in stilbene **12** (Entry 8, Table 2) where the proportion of bisindoline is significantly

increased. In the present study, replacement of butyramide (**5**) with isobutyrylamide (**6**) resulted in a lowering of the yield of indoline **15** to 29%. Bisindoline formation was not observed, a result that is all the more remarkable when compared to stilbene **12** (Entry 8, Table 2).

2.2. Effect of Amide Structure on the Radical Cyclization Leading to Indoline Formation

The very different behaviour of **5** and **6** on exposure to FeCl₃ is readily explained by the early transition state pictures **I** and **II** (Scheme 3) where the increase steric bulk of the isobutyrylamide renders cyclization more difficult, hence the lower yield of **15** (29%). A similar explanation would account for the low yield of indoline **17** from stilbene **8**.

Scheme 3. Early transition state pictures for radical cyclization leading to indoline formation.



With respect to stilbenes **7** and **11**, cyclization proceeding via radical cation **13a** leading to **16** and **20a** respectively, is slightly more favoured for stilbene **11** (furancarboxamide) than for stilbene **7** (benzamide) on stereoelectronic grounds [16], as the transition state pictures **III** and **IV** demonstrate (Scheme 3). We believe that the coplanar orientation of furan and carbonyl groups means that cyclization experiences less resistance in the case of **11**. This coplanarity seems less likely for stilbene **7** (see III and IV, Scheme 3). The stereoelectronic factor also helps to explain the fact that bisindoline formation (**20b** and **21b**) is observed with stilbenes **11** and **12** but not with stilbene **7** (see discussion in

Section 2.3 and Scheme 10). In the case of stilbene **9**, cyclization is made more difficult (and hence the significantly reduced yield) because it must proceed via radical cation **13b**. It is noteworthy that the C(8) carbon of **9**, in this special case, is more shielded than the C(7) (compared to the other furancarboxamidostilbenes) because of the directional nature and electron withdrawing tendency of the 2-methoxy lone electron pairs [13]. In the case of stilbene **10**, radical cation **13b** is again the crucial intermediate (see Ref. [10] for the similar case of 10-acetamido-3-methoxystilbene) [15]. It may be worth emphasising that the FeCl₃ oxidation of stilbenes **9** and **10** proceed via a different radical cations (analogous to **13b**) whereas stilbene **12** proceeds via radical cation **13a** (see Table 2). This is because stilbene **12** on oxidation produces a radical cation in which the positive charge is at C(7) as a result of mesomeric stabilization from a *para*-methoxy substituent. By contrast in stilbene **10** where the methoxy group is *meta*, the position of the positive charge changes to C(8) because of superior mesomeric stabilization which comes from the amide nitrogen lone pair in the *ortho* position (*i.e.*, a C-10 amido group). In the case of stilbene **9** where mesomeric stabilization of a C(7) carbocation (in the radical cation) might have been expected, we observed a unique *ortho*-methoxy lone pair effect which dramatically reverses the position of radical and positive charge. The positive charge is now at C(8) rather than at C(7). This electronic factor is seen even in the NMR of the stilbenes (see Table 1). Notice that remarkably in stilbene **9** the C(7) proton is substantially more deshielded than C(8). The phenomena described above underpin the mechanistic interpretation discussed in Schemes 11 to 13. It is significant that in contrast to our first report (Scheme 1) where the bisindoline **4A** was presented in the *meso* arrangement, in this report all bisindolines are designated as racemic. The reason for this is explained in Section 2.3.

2.3. Dimerization Pathways and PM6 Calculations for the Minor Products

The basis for the observed stereoselectivity for each of the bisindoline minor products (**14b**, **20b** and **21b**) is explained below. There are four diastereomeric possibilities. The PM6 calculations (MOPAC2009) are provided in Tables 3-5.

Table 3. PM6 calculation for **14b**.

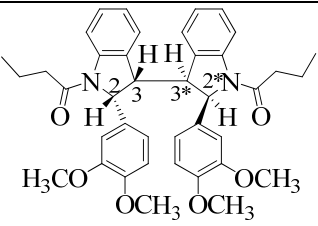
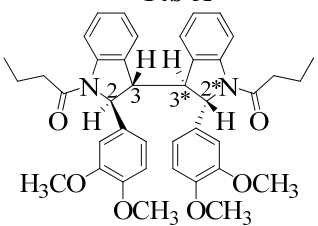
Stereoisomer	Symmetry element	Heat of Formation (kcal/mol)	H2-H3	H2*-H3*	H3-H3*
 <p>14b-A</p>	C ₂ axis	-154.22	19.15	346.41	156.58
 <p>14b-B</p>	C ₂ axis	-162.78	250.79	250.79	171.63

Table 3. Cont.

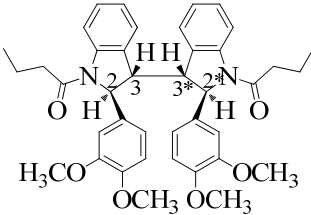
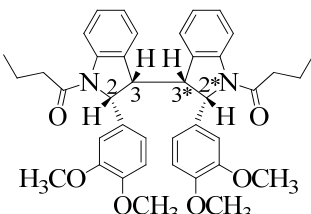
 <p style="text-align: center;">14b-C</p>	Plane (Meso)	-163.46	240.71	111.62	298.43
 <p style="text-align: center;">14b-D</p>	Plane (Meso)	-133.96	310.52	324.60	24.01

Table 4. PM6 calculation for 20b.

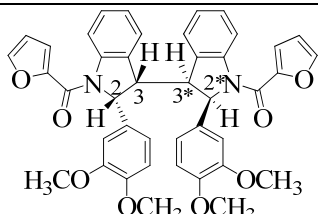
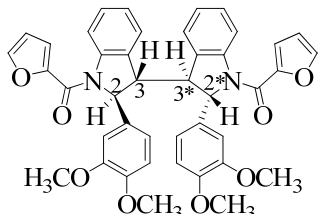
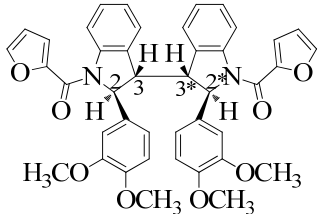
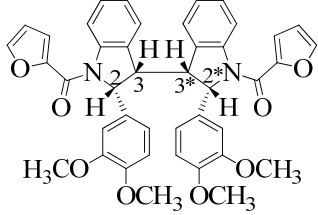
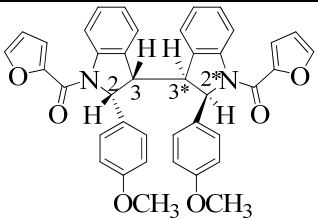
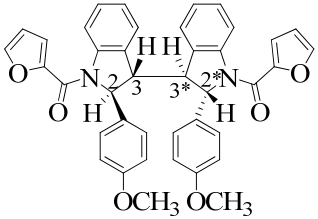
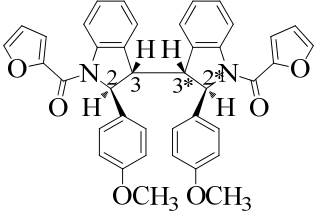
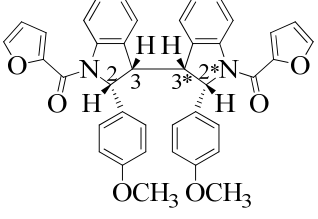
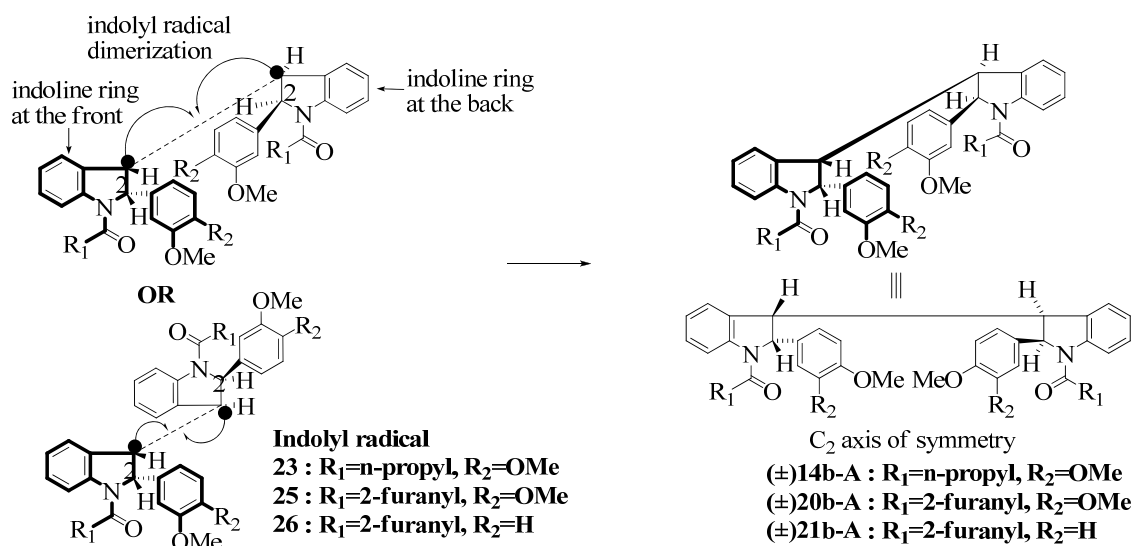
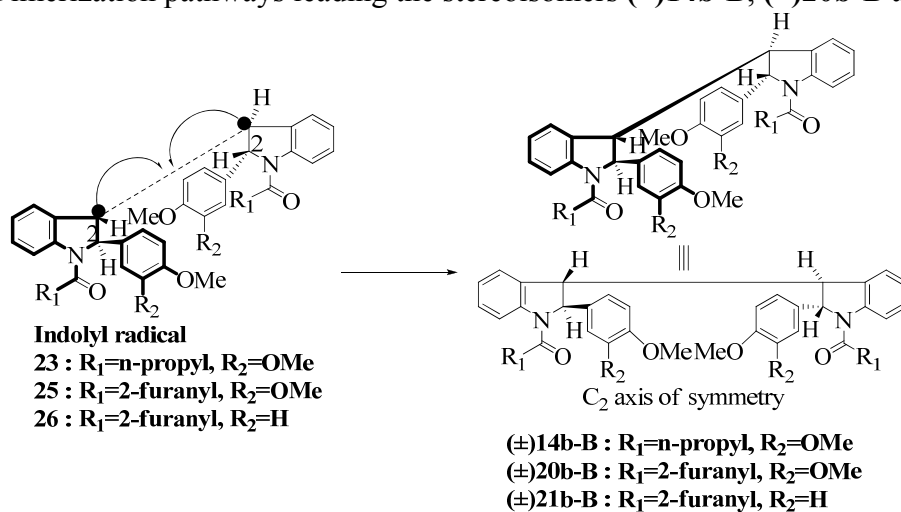
Stereoisomer	Symmetry element	Heat of Formation (kcal/mol)	H2-H3	H2*-H3*	H3-H3*
 <p style="text-align: center;">20b-A</p>	C ₂ axis	-116.85	348.44	348.44	155.06
 <p style="text-align: center;">20b-B</p>	C ₂ axis	-123.76	241.19	241.17	120.43
 <p style="text-align: center;">20b-C</p>	Plane (Meso)	-126.41	-111.73	119.11	61.86
 <p style="text-align: center;">20b-D</p>	Plane (Meso)	-115.76	352.90	26.21	65.36

Table 5. PM6 calculation for 21b.

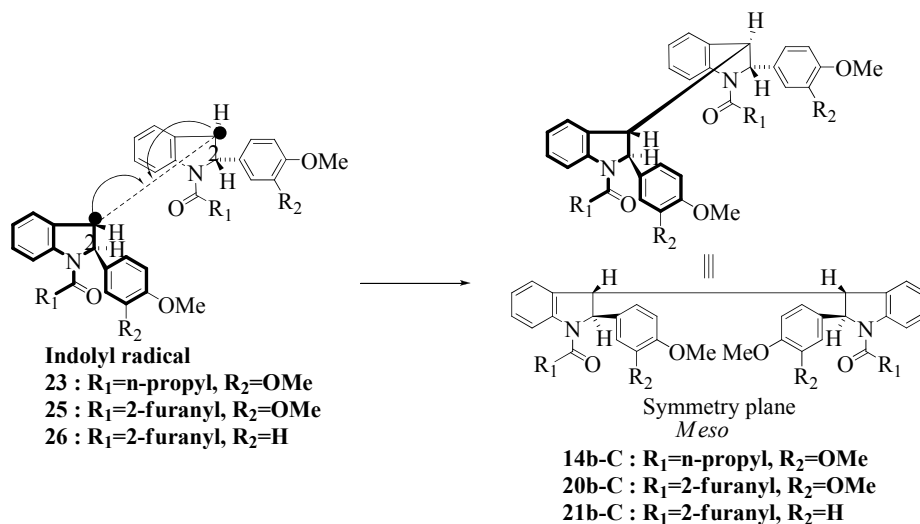
Stereoisomer	Symmetry element	Heat of Formation (kcal/mol)	H2-H3	H2*-H3*	H3-H3*
 <p>21b-A</p>	C ₂ axis	-48.59	340.27	340.27	115.07
 <p>21b-B</p>	C ₂ axis	-55.04	247.75	247.23	172.63
 <p>21b-C</p>	Plane (Meso)	-56.28	240.70	111.61	298.43
 <p>21b-D</p>	Plane (Meso)	-43.83	12.48	26.33	69.76

Scheme 4. Dimerization pathways leading the stereoisomers (±)14b-A, (±)20b-A and (±)21b-A.

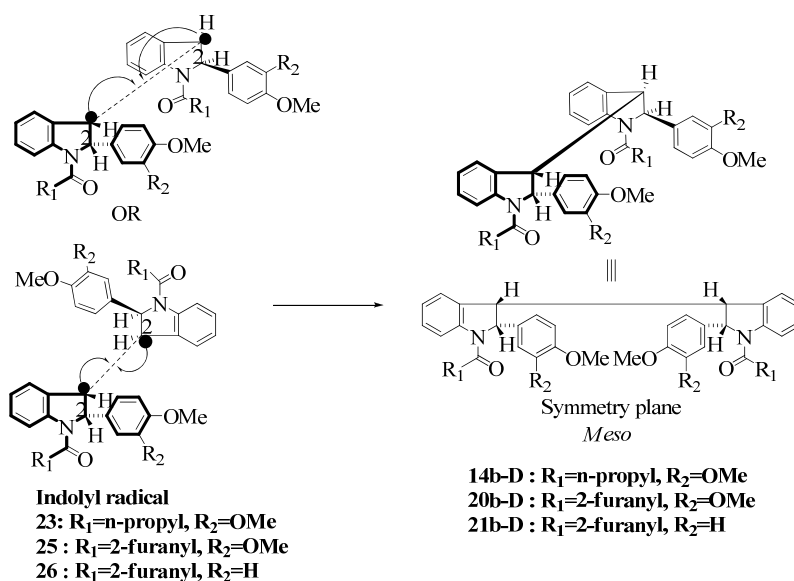


Scheme 5. Dimerization pathways leading the stereoisomers (\pm)14b-B, (\pm)20b-B and (\pm)21b-B.

Scheme 6. Dimerization pathways leading the stereoisomers 14b-C, 20b-C and 21b-C.

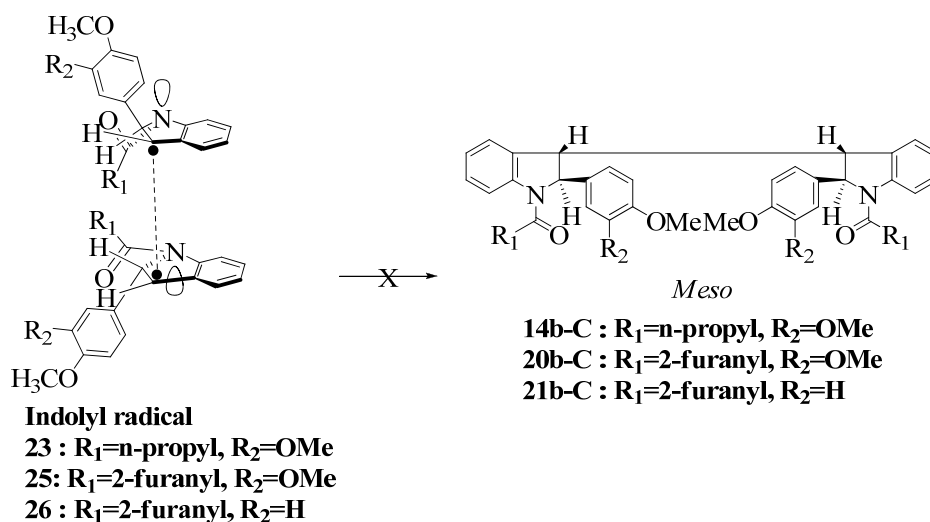


Scheme 7. Dimerization pathways leading the stereoisomers 14b-D, 20b-D and 21b-D.



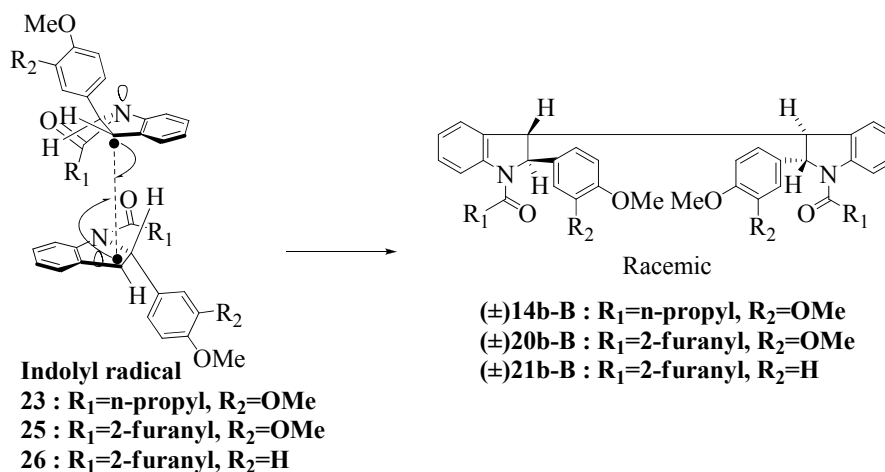
These calculations (the thermodynamic argument) lead to the same conclusions as the mechanistic analysis of dimerization pathways for the various indolyl radicals (the kinetic argument) see Scheme 4 to Scheme 7.

Scheme 8. Another perspective on dimerization pathways leading to the stereoisomer **14b-C**, **20b-C** and **21b-C**.



The arguments that distinguish (\pm)**14b-B** and *meso* **14b-C** (Table 3) are more finely balanced as these two diastereoisomers are closer in energy (-162.78 and -163.46 kcal/mol). This closeness is also reflected in the fact that in examining dimerization pathways for the indolyl radicals (Schemes 5 and 6), dimerization appears to be equally feasible in both cases. In comparing the early transition state pictures in Schemes 8 and 9, the approach of indolyl radicals in Scheme 9 would have the effect of keeping the “phenyl” region of the indoline rings as far apart as possible, as well as possibly minimizing interactions between the amide moieties (see Scheme 8). This would appear to lead to the conclusion that the correct stereostructures are (\pm)**14b-B**, (\pm)**20b-B** and (\pm)**21b-B** respectively (see Scheme 9 and Table 2).

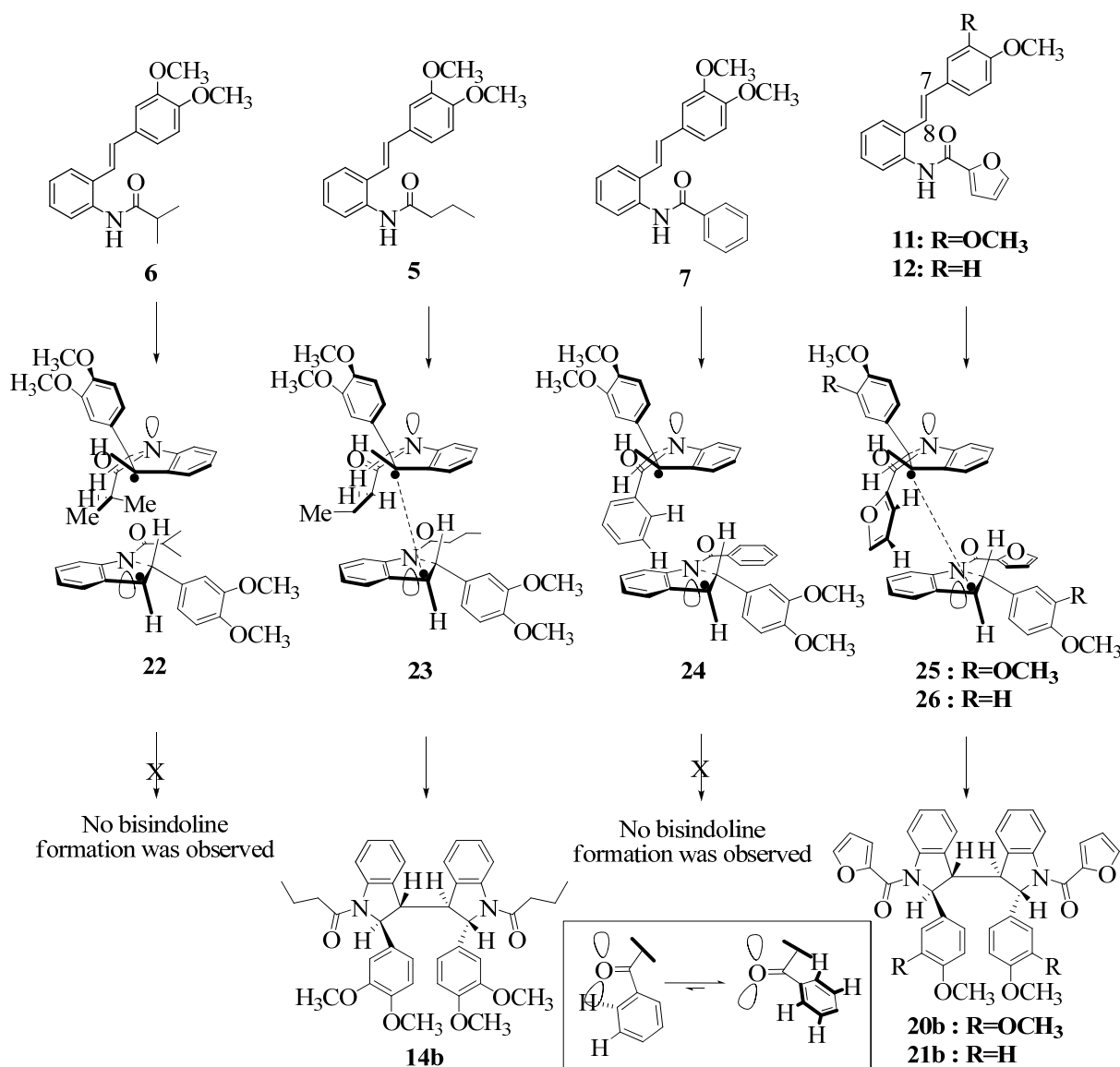
Scheme 9. Another perspective on dimerization pathways leading to the stereoisomer (\pm)**14b-B**, (\pm)**20b-B** and (\pm)**21b-B**.



One additional point of some importance relates to the PM6 calculations. Although (\pm)**14b-B** is slightly higher in energy, the dihedral angles in this case are consistent with the symmetrical nature of the molecule (Table 3) and is therefore to be preferred over the *meso* form **14b-C** (Scheme 8). These arguments fully justify the exploitation of PM6 calculations for the elucidation of stereochemical problems inherent in reactions of this type.

Exactly analogous arguments can be used to justify the presentation of bisindolines **20b** and **21b** which carry furancarboxamide moieties, as their racemic modifications (Tables 2, 4 and 5). For **20b-A**, **20b-D**, **21b-A** and **21b-D** are readily ruled out on energetic grounds and this thermodynamic argument is again amply vindicated by the dimerization pathways for the indolyl radicals. Consideration of indolyl radical dimerization pathways and thermodynamic arguments favour formation of (\pm)**20b-B** and **20b-C** (Schemes 5 and 6) and (\pm)**21b-B** and **21b-C** (Schemes 5 and 6).

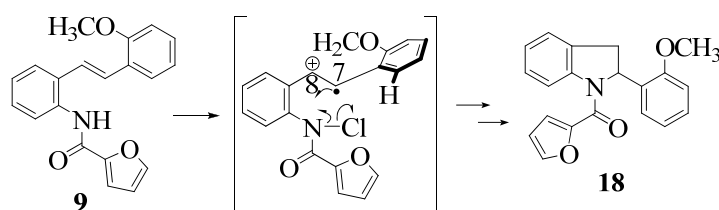
Scheme 10. Effect of amide structure on the dimerization of indolyl radical **22-26** leading to bisindoline formation.



However careful scrutiny of the dimerization pathways as previously described (Schemes 9 and 10) inevitably leads to the conclusion that the correct stereostructures are (\pm)**20b-B** and (\pm)**21b-B**. These conclusion are supported by the X-ray data for the bisindoline depicted in Scheme 1 and confirm that the bisindoline has the structure (\pm)**4b** (and not **4a** as originally reported by us).

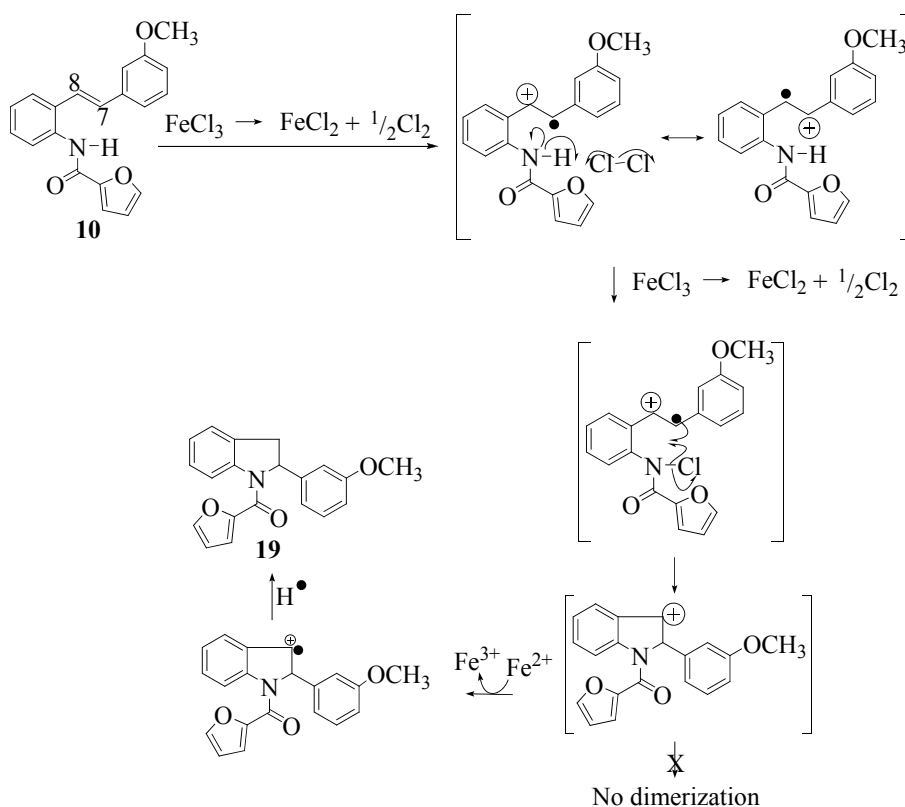
With respect to bisindoline formation, it would seem that in the presumably early transition states involving the corresponding indolyl radicals **22** and **23** (Scheme 10), the methyl group of the isobutryl moiety in **22** is able to block dimerization so that no bisindoline is obtained. By contrast indolyl radical **23** by virtue of possessing an *n*-butyrylamido group has only the much smaller H in that position and dimerization is not impeded.

Scheme 11. The *ortho*-methoxy effect.



In the case of the **9** (Scheme 11), the attempted dimerization fails in spite of the fact that one would have expected a radical cation intermediate analogous to **13a** (Table 2). The reduced nucleophilicity of this NH and the reduced electron density in the olefinic bond may well account for the low yield of the indoline **18** (Scheme 10) (see our previous discussion on NMR spectroscopic characteristics for the eight stilbenes) [13].

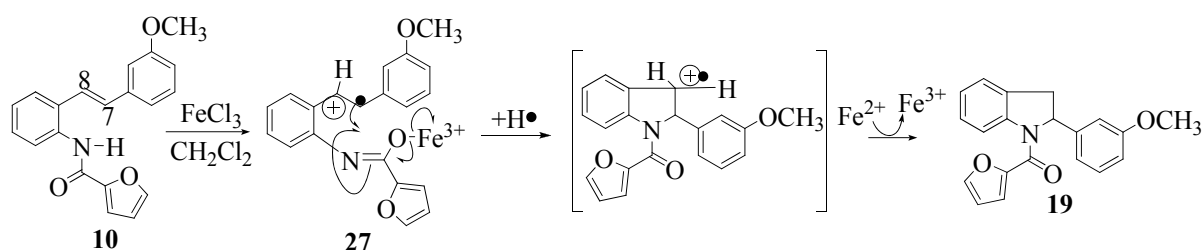
Scheme 12. Mechanistic interpretation I.



It is interesting to note that in **9** the C7-H ($\delta 7.40$) is more deshielded than the C8-H ($\delta 7.29$) in contrast to the other furan carboxamidostilbenes **10**, **11** and **12**. This would have the effect of reversing the position of the radical and cation (formed after oxidation) where the removal of an electron from C8 would be preferred.

The failure of dimerization in the case of **10** is due to the formation of the radical cation analogous to **13b** (Table 2) and Scheme 12. The formation of this radical cation is related to the absence of a paramethoxy group (in **10**) that could stabilize a C7 cation and as a result the cation is formed preferentially at C8. Ring closure proceeds possibly via homolysis of an N-Cl bond leading to the nitrogen centred radical as shown in Scheme 12 or alternatively, via the Fe^{3+} azaenolate (**27**). Reduction of the indolyl cation (whose formation renders dimerization impossible) to the indolyl radical cation and $\text{H}\cdot$ uptake leads to the indoline. This pathway is shown in Scheme 13.

Scheme 13. Mechanistic interpretation II.



3. Experimental

3.1. General

Unless otherwise noted, materials were purchased from commercial suppliers and used without purification. THF was freshly distilled from calcium hydride. DMF was dried over 4Å molecular sieves (Sigma-Aldrich) prior to use. Column chromatography was performed using Merck silica gel (0.040–0.063 mm). For thin layer chromatography, Merck TLC aluminum sheets (silica gel 60 F₂₅₄) were used; centrifugal chromatography, Merck silica gel 60 PF₂₅₄ containing gypsum were used. Infrared spectra were recorded on a Perkin Elmer FTIR Spectrum RX-1 spectrometer at wavenumbers from 4000–400 cm^{-1} . Nuclear magnetic resonance (NMR) spectra were obtained on a JEOL JNM-LA 400 and JEOL ECA-400 instrument. Spectra are reported in units of ppm on the scale, relative to chloroform and the coupling constants are given in Hz. Ultraviolet (UV) spectra were recorded from 190–400 nm, in methanol, on a Shimadzu UV-Visible Spectrophotometer 1650. Mass spectra were measured using an Agilent 6530 Accurate-Mass Q-TOF LC/MS system. Detailed experimental procedures for the synthesis of stilbenes **7-14** and starting materials have been reported elsewhere [13].

3.2. General Procedure for the FeCl_3 Oxidative Coupling

Stilbene (1 equiv) was dissolved in CH_2Cl_2 (25 mL). ‘Anhydrous’ FeCl_3 (2-3 equiv) was added to the mixture under nitrogen. The mixture was stirred at room temperature and monitored by TLC. After the consumption of the stilbene, the mixture was diluted with aqueous ammonium chloride solution and extracted with ethyl acetate (3×25 mL). The combined organic fractions were dried over

anhydrous sodium sulphate. Purification of the crude product by column chromatography afforded the desired products. Semi-empirical molecular orbital calculations were performed to optimise the geometry of the molecules using the PM6 method [17] included in MOPAC2009 [18].

3.2.1. 1-(2-(3,4-Dimethoxyphenyl)indolin-1-yl)butan-1-one (**14a**)

Yield 0.30 g (63%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 2961, 1659, 1516, 1480, 1463, 1401, 1262, 1139, 1027, 754; λ_{\max} (MeOH)/nm: 237, 253, 281; $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ_{H} 8.33 (d, $J = 7.6$ Hz, H-8, 1H), 7.24 (t, $J = 7.8$ Hz, H-7, 1H), 7.12 (d, $J = 6.4$ Hz, H-5, 1H), 7.03 (t, $J = 7.6$ Hz, H-6, 1H), 6.76 (d, $J = 8.2$ Hz, H-5', 1H), 6.68 (d, $J = 8.2$ Hz, H-6', 1H), 6.64 (s, H-2', 1H), 5.36 (d, $J = 7.3$ Hz, H-2, 1H), 3.83 (s, OCH_3 , 3H), 3.77 (s, OCH_3 , 3 α , 4H), 2.94 (d, $J = 16.5$ Hz, H-3 β , 1H), 2.09-2.36 (m, H-2'', CH_2 , 2H), 1.67 (s, H-3'', CH_2 , 2H), 0.84 (s, H-4'', CH_3 , 3H); $^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ_{C} 172.0 (C-1''), 149.5 (C-3'), 148.5 (C-4'), 143.5 (C-9), 136.0 (C-1'), 129.3 (C-4), 127.8 (C-7), 125.1 (C-5), 124.0 (C-6), 117.2 (C-6'), 117.0 (C-8), 111.4 (C-5'), 108.0 (C-2'), 62.6 (C-2), 56.0 (OCH_3), 55.9 (OCH_3), 39.2 (CH_2 , C-3), 37.5 (CH_2 , C-2''), 18.2 (CH_2 , C-3''), 13.9 (CH_3 , C-4''); HRMS (+ESI) $[\text{M}+\text{H}]^+$: 326.1754, $\text{C}_{20}\text{H}_{24}\text{NO}_3$ requires 326.1756.

3.2.2. 1,1'-2,2'- bis(3,4-Dimethoxyphenyl)- 3,3'- biindoline-1,1'-diyl dibutan-1-one ((\pm)**14b**)

Yield 0.06 g (6%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 2961, 1666, 1516, 1462, 1398, 1255, 1140, 1027, 755; λ_{\max} (MeOH)/nm: 237, 249, 281; $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ_{H} 8.53 (d, $J = 8.2$ Hz, H-8, H-8*, 2H), 7.46 (t, $J = 8.0$ Hz, H-7, H-7*, 2H), 7.30 (d, $J = 7.3$ Hz, H-5, H-5*, 2H), 7.21 (t, $J = 7.3$ Hz, H-6, H-6*, 2H), 6.61 (d, $J = 8.7$ Hz, H-5', H-5'*, 2H), 6.21 (d, $J = 7.8$ Hz, H-6', H-6'*, 2H), 5.81 (s, H-2', H-2'*, 2H), 4.70 (s, H-2, H-2*, CH , 2H), 3.77 (s, 2 X OCH_3 , 6H), 3.61 (s, 2 X OCH_3 , 6H), 3.52 (s, H-3, H-3*, CH , 2H), 1.83-2.12 (m, H-2'', H-2''*, CH_2 , 4H), 1.45-1.56 (m, H-3'', H-3''*, CH_2 , 4H), 0.76 (t, $J = 7.6$ Hz, H-4'', H-4''*, CH_3 , 6H); $^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ_{C} 172.4 (C-1'', C-1''*), 149.4 (C-3', C-3'*), 148.3 (C-4', C-4'*), 144.3 (C-9, C-9*), 134.7 (C-1', C-1'*), 130.0 (C-4, C-4*), 129.4 (C-7, C-7*), 125.3 (C-5, C-5*), 124.5 (C-6, C-6*), 117.7 (C-8, C-8*), 115.9 (C-6', C-6'*), 111.3 (C-5', C-5'*), 107.5 (C-2', C-2'*), 63.4 (C-2, C-2*), 56.9 (C-3, C-3*), 55.9 (2 X OCH_3), 55.8 (2 X OCH_3), 37.1 (CH_2 , C-2'', C-2''*), 17.7 (CH_2 , C-3'', C-3''*), 13.8 (CH_3 , C-4'', C-4''*); HRMS (+ESI) $[\text{M}+\text{H}]^+$: 649.3276, $\text{C}_{40}\text{H}_{44}\text{N}_2\text{O}_6$ requires 649.3278.

3.2.3. 1-(2-(3,4-dimethoxyphenyl)indolin-1-yl)-2-methylpropan-1-one (**15**)

Yield 0.13 g (29%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 2964, 1653, 1516, 1479, 1263, 1138, 1026, 755; λ_{\max} (MeOH)/nm: 210, 238, 253, 281; $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ_{H} 8.36 (d, $J = 5.5$ Hz, H-8, 1H), 7.24 (t, $J = 7.8$ Hz, H-7, 1H), 7.11 (d, $J = 7.3$ Hz, H-5, 1H), 7.02 (t, $J = 7.8$ Hz, H-6, 1H), 6.75 (d, $J = 8.2$ Hz, H-5', 1H), 6.68 (dd, $J = 8.2$ Hz, 1.8 Hz, H-6', 1H), 6.64 (s, H-2', 1H), 5.43 (d, $J = 8.7$ Hz, H-2, 1H), 3.82 (s, OCH_3 , 3H), 3.77 (s, OCH_3 , H-3 α , 4H), 2.96 (d, $J = 16.0$, H-3 β , 1H), 2.61 (s, H-2'', 1H), 1.20 (d, $J = 6.9$ Hz, H-4'', 3H), 0.87 (s, H-3'', 1H); $^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ_{C} 177.0 (C-1''), 149.5 (C-3'), 148.5 (C-4'), 143.5 (C-9), 136.3 (C-1'), 129.4 (C-4), 127.8 (C-7), 125.0 (C-5), 124.1 (C-6), 117.3 (C-8), 117.1 (C-6'), 111.4 (C-5'), 108.0 (C-2'), 62.4 (C-2), 56.0 (2 x OCH_3), 39.1 (CH_2 , C-3),

33.4 (CH, C-2''), 20.3 (CH₃, C-4''), 19.1 (CH₃, C-3''); HRMS (+ESI) [M+H]⁺: 326.1760, C₂₀H₂₄NO₃ requires 326.1751.

3.2.4. (2-(3,4-Dimethoxyphenyl)indolin-1-yl)(phenyl)methanone (16)

Yield 0.21 g (40%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 2956, 1646, 1516, 1480, 1386, 1259, 1139, 1026, 755; λ_{\max} (MeOH)/nm: 216, 267; ¹H-NMR (400 MHz; CDCl₃) δ_{H} 7.38 (t, $J = 6.8$ Hz, H-5'', 1H), 7.17-7.31 (m, H-5, H-7, H-8, H-3'', H-4'', H-6'', H-7'', 7H), 7.06 (t, $J = 7.3$ Hz, H-6, 1H), 6.68 (d, $J = 8.2$ Hz, H-5', 1H), 6.55 (d, $J = 5.0$ Hz, H-6', 1H), 6.42 (s, H-2', 1H), 5.37 (s, H-2, 1H), 3.81 (s, OCH₃, 3H), 3.67-3.74 (m, OCH₃, H-3 α , 4H), 2.98 (dd, $J = 16.2$ Hz, 1.8 Hz, H-3 β , 1H); ¹³C-NMR (100 MHz; CDCl₃) δ_{C} 169.9 (C-1''), 149.0 (C-3'), 148.3 (C-4'), 143.2 (C-9), 137.1 (C-2''), 136.2 (C-1'), 130.7 (C-4), 130.0 (C-5''), 128.3 (C-4'', C-6''), 127.6 (C-7), 127.0 (C-3'', C-7''), 125.3 (C-5, C-8), 124.4 (C-6), 117.5 (C-6'), 111.3 (C-5'), 108.9 (C-2'), 64.3 (C-2), 55.9 (OCH₃), 55.8 (OCH₃), 38.5 (C-3); HRMS (+ESI) [M+Na]⁺: 382.1416, C₂₃H₂₁NNaO₃ requires 382.1414.

3.2.5. Cyclohexyl(2-(3,4-dimethoxyphenyl)indolin-1-yl)methanone (17)

Yield 0.13 g (12%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 2930, 1655, 1516, 1479, 1403, 1265, 1138, 1027, 754; λ_{\max} (MeOH)/nm: 216, 237, 254, 282; ¹H-NMR (400 MHz; CDCl₃) δ_{H} 8.35 (d, $J = 6.4$ Hz, H-8, 1H), 7.24 (t, $J = 8.1$ Hz, H-7, 1H), 7.11 (d, $J = 6.6$ Hz, H-5, 1H), 7.03 (t, $J = 7.4$ Hz, H-6, 1H), 6.76 (d, $J = 8.3$ Hz, H-5', 1H), 6.70 (dd, $J = 8.2$ Hz, 1.7 Hz, H-6', 1H), 6.65 (s, H-2', 1H), 5.42 (d, $J = 7.6$ Hz, H-2, 1H), 3.83 (s, OCH₃, 3H), 3.77 (s, OCH₃, H-3 α , 4H), 2.97 (d, $J = 15.8$, H-3 β , 1H), 2.34 (s, H-2'', 1H), 1.20-1.89 (m, 5 x CH₂, 10H); ¹³C-NMR (100 MHz; CDCl₃) δ_{C} 175.9 (C-1''), 149.3 (C-3'), 148.4 (C-4'), 143.5 (C-9), 136.5 (C-1'), 129.4 (C-4), 127.7 (C-7), 124.8 (C-5), 123.7 (C-6), 117.1 (C-8, C-5'), 111.4 (C-6'), 108.0 (C-2'), 62.3 (C-2), 55.8 (2 x OCH₃), 43.8 (CH, C-2''), 38.9 (CH₂, C-3), 30.0, 28.7, 26.0, 25.6, 25.4 (5 x CH₂); HRMS (+ESI) [M+H]⁺: 366.2065, C₂₃H₂₇NO₃ requires 366.2064.

3.2.6. Furan-2-yl(2-(2-methoxyphenyl)indolin-1-yl)methanone (18)

Yield 0.07 g (11%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 3007, 1634, 1479, 1397, 1243, 1025, 832, 753; λ_{\max} (MeOH)/nm: 280, 297; ¹H-NMR (400 MHz; CDCl₃) δ_{H} 8.33 (s, H-8, 1H), 7.36 (d, $J = 1.8$ Hz, H-5'', 1H), 7.28 (t, $J = 7.8$ Hz, H-7, 1H), 7.17 (td, $J = 7.8$ Hz, 1.8 Hz, H-4', 1H), 7.12 (d, $J = 7.3$ Hz, H-5, 1H), 7.06 (td, $J = 7.6$ Hz, 0.9 Hz, H-6, 1H), 6.98 (dd, $J = 7.6$ Hz, 1.8 Hz, H-6', 1H), 6.89 (d, $J = 8.2$ Hz, H-3', 1H), 6.80 (d, $J = 3.2$ Hz, H-3'', 1H), 6.75 (t, $J = 7.5$ Hz, H-5', 1H), 6.33 (dd, $J = 3.7$ Hz, 1.8 Hz, H-4'', 1H), 6.31 (dd, $J = 9.8$ Hz, 1.4 Hz, H-2, 1H), 3.92 (s, OCH₃, 3H), 3.76 (dd, $J = 16.2$ Hz, 10.1 Hz, H-3 α , 1H), 2.90 (dd, $J = 16.5$ Hz, 1.4 Hz, H-3 β , 1H); ¹³C-NMR (100 MHz; CDCl₃) δ_{C} 158.2 (C-1''), 155.5 (C-2'), 147.8 (C-2''), 144.5 (C-5''), 143.7 (C-9), 131.6 (C-1'), 130.7 (C-4), 128.4 (C-4'), 127.6 (C-7), 125.2 (C-5), 125.0 (C-6'), 124.7 (C-6), 120.8 (C-5'), 118.1 (C-8), 116.5 (C-3''), 111.5 (C-4''), 110.5 (C-3'), 58.9 (C-2), 55.6 (OCH₃), 38.2 (C-3); HRMS (+ESI) [M+Na]⁺: 342.1106, C₂₀H₁₇NNaO₃ requires 342.1101.

3.2.7. Furan-2-yl(2-(3-methoxyphenyl)indolin-1-yl)methanone (**19**)

Yield 0.04 g (38%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 3006, 1634, 1479, 1397, 1286, 1048, 755; λ_{\max} (MeOH)/nm: 281, 296; $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ_{H} 8.24 (s, H-8, 1H), 7.39 (s, H-5", 1H), 7.27 (t, $J = 8.2$ Hz, H-7, 1H), 7.12-7.16 (m, H-5, H-5', 2H), 7.07 (t, $J = 7.6$ Hz, H-6, 1H), 6.91 (d, $J = 3.7$ Hz, H-3", 1H), 6.69-6.75 (m, H-2', H-4', H-6', 3H), 6.36 (dd, $J = 3.4$ Hz, 1.8 Hz, H-4", 1H), 6.05 (dd, $J = 9.6$ Hz, 1.4 Hz, H-2, 1H), 3.78 (dd, $J = 15.8$ Hz, 9.6 Hz, H-3 α , CH₂, 1H), 3.69 (s, OCH₃, 3H), 3.01 (d, $J = 15.6$ Hz, H-3 β , CH₂, 1H); $^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ_{C} 159.9 (C-3'), 158.3 (C-1"), 148.0 (C-2"), 145.5 (C-1'), 144.3 (C-5"), 143.6 (C-9), 130.0 (C-4, C-5'), 127.8 (C-7), 125.1 (C-5), 124.8 (C-6), 117.9 (C-8), 117.3 (C-4'), 117.1 (C-3"), 112.4 (C-6'), 111.7 (C-4"), 111.0 (C-2'), 63.3 (C-2), 55.2 (OCH₃), 39.3 (C-3); HRMS (+ESI) $[\text{M}+\text{H}]^+$: 320.1286, C₂₀H₁₈NO₃ requires 320.1281.

3.2.8. (2-(3,4-Dimethoxyphenyl)indolin-1-yl)(furan-2-yl)methanone (**20a**)

Yield 0.15 g (46%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 3008, 1634, 1479, 1397, 1257, 1140, 1026, 754; λ_{\max} (MeOH)/nm: 207, 283, 296; $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ_{H} 8.21 (d, $J = 5.5$ Hz, H-8, 1H), 7.41 (dd, $J = 1.8$ Hz, 0.92 Hz, H-5", 1H), 7.26 (t, $J = 7.8$ Hz, H-7, 1H), 7.16 (d, $J = 7.8$ Hz, H-5, 1H), 7.07 (td, $J = 7.6$ Hz, 0.92 Hz, H-6, 1H), 6.89 (d, $J = 3.6$ Hz, H-3", 1H), 6.63-6.68 (m, H-2', H-5', H-6', 3H), 6.36 (dd, $J = 3.4$ Hz, 1.4 Hz, H-4", 1H), 6.02 (dd, $J = 9.6$ Hz, 1.8 Hz, H-2, CH, 1H), 3.76-3.82 (m, H-3 α , OCH₃, 4H), 3.73 (s, OCH₃, 3H), 3.01 (dd, $J = 16.0$ Hz, 1.84 Hz, H-3 β , CH₂, 1H); $^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ_{C} 158.5 (C-1"), 149.1 (C-3'), 148.3 (C-4'), 148.1 (C-2"), 144.1 (C-5"), 143.5 (C-9), 136.4 (C-1'), 130.1 (C-4), 127.7 (C-7), 125.1 (C-5), 124.7 (C-6), 117.7 (C-8), 117.1 (C-5'), 117.0 (C-3"), 111.7 (C-4"), 111.3 (C-6'), 108.2 (C-2'), 63.1 (C-2), 55.9 (2 x OCH₃), 39.4 (C-3); HRMS (+ESI) $[\text{M}+\text{H}]^+$: 350.1404, C₂₁H₂₀NO₄ requires 350.1387; $[\text{M}+\text{Na}]^+$: 372.1215, C₂₁H₁₉NNaO₄ requires 372.1206.

3.2.9. (2,2'- bis(3,4-Dimethoxyphenyl)-3,3'-biindoline-1,1'-diyl)-bis(furan-2-ylmethanone) ((\pm))**20b**)

Yield 0.07 g (10%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 2934, 1636, 1516, 1476, 1394, 1254, 1141, 1025, 754; λ_{\max} (MeOH)/nm: 207, 283; $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ_{H} 8.59 (d, $J = 7.8$ Hz, H-8, H-8*, 2H), 7.48 (td, $J = 7.8$ Hz, 1.4 Hz, H-7, H-7*, 2H), 7.36 (d, $J = 7.3$ Hz, H-5, H-5*, 2H), 7.23-7.27 (m, H-6, H-6*, H-5", H-5"*, 4H), 6.67 (d, $J = 3.6$ Hz, H-3", H-3"*, 2H), 6.54 (d, $J = 8.2$ Hz, H-5', H-5'*, 2H), 6.28 (d, $J = 1.8$ Hz, H-6', H-6'*, 2H), 6.21 (dd, $J = 3.4$ Hz, 1.8 Hz, H-4", H-4"*, 2H), 5.83 (d, $J = 1.8$ Hz, H-2', H-2'*, 2H), 5.78 (s, H-2, H-2*, CH, 2H), 3.70 (s, 2 x OCH₃, 6H), 3.60 (s, H-3, H-3*, 2H), 3.57 (s, 2 x OCH₃, 6H); $^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ_{C} 158.4 (C-1", C-1"*), 149.1 (C-3', C-3'*), 148.1 (C-4', C-4'*), 147.4 (C-2", C-2"*), 144.9 (C-9, C-9*), 144.6 (C-5", C-5"*), 135.6 (C-1', C-1'*), 130.8 (C-4, C-4*), 129.2 (C-7, C-7*), 125.4 (C-5, C-5*), 125.0 (C-6, C-6*), 118.2 (C-8, C-8*), 117.3 (C-3", C-3"*), 115.9 (C-6', C-6'*), 111.5 (C-4", C-4"*), 111.1 (C-5', C-5'*), 107.6 (C-2', C-2'*), 63.6 (C-2, C-2*), 57.3 (C-3, C-3*), 55.81 (2 x OCH₃), 55.76 (2 x OCH₃); HRMS (+ESI) $[\text{M}+\text{H}]^+$: 697.2542, C₄₂H₃₇N₂O₈ requires 697.2544.

3.2.10. Furan-2-yl(2-(4-methoxyphenyl)indolin-1-yl)methanone (**21a**)

Yield 0.10 g (21%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 3005, 1635, 1513, 1478, 1397, 1249, 1179, 1034, 834, 755; λ_{\max} (MeOH)/nm: 203, 226, 283, 297; $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ_{H} 8.25 (d, $J = 4.6$ Hz, H-8, 1H), 7.40 (dd, $J = 1.8$ Hz, 0.92 Hz, H-5", 1H), 7.27 (t, $J = 7.8$ Hz, H-7, 1H), 7.16 (d, $J = 7.8$ Hz, H-5, 1H), 7.04-7.09 (m, H-6, H-2', H-6', 3H), 6.90 (d, $J = 4.1$ Hz, H-3", 1H), 6.72-6.75 (m, H-3', H-5', 2H), 6.35 (dd, $J = 3.7$ Hz, 1.8 Hz, H-4", 1H), 6.05 (dd, $J = 9.6$ Hz, 1.8 Hz, H-2, CH, 1H), 3.76 (dd, $J = 16.0$ Hz, 10.1 Hz, H-3 α , CH₂, 1H), 3.70 (s, OCH₃, 3H), 2.98 (dd, $J = 16.0$ Hz, 1.4 Hz, H-3 β , CH₂, 1H); $^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ_{C} 158.8 (C-4'), 158.4 (C-1"), 148.1 (C-2"), 144.2 (C-5"), 143.6 (C-9), 136.0 (C-1'), 130.1 (C-4), 127.7 (C-7), 126.1 (C-2', C-6'), 125.1 (C-5), 124.7 (C-6), 117.8 (C-8), 117.0 (C-3"), 114.2 (C-3', C-5'), 111.7 (C-4"), 62.8 (C-2), 55.3 (OCH₃), 39.4 (C-3); HRMS (+ESI) $[\text{M}+\text{H}]^+$: 320.1294, C₂₀H₁₈NO₃ requires 320.1281; $[\text{M}+\text{Na}]^+$: 342.1105, C₂₀H₁₇NNaO₃ requires 342.1101.

3.2.11. (2,2'- bis(4-methoxyphenyl)- 3,3'- biindoline-1,1'-diyl) bis(furan-2-ylmethanone) ((±)**21b**)

Yield 0.11 g (12%); $\nu_{\max}/\text{cm}^{-1}$ (NaCl): 3008, 1636, 1512, 1477, 1395, 1249, 1177, 1034, 755; λ_{\max} (MeOH)/nm: 205, 226, 284; $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ_{H} 8.59 (d, $J = 8.2$ Hz, H-8, H-8*, 2H), 7.49 (td, $J = 7.8$ Hz, 1.4 Hz, H-7, H-7*, 2H), 7.31 (d, $J = 6.4$ Hz, H-5, H-5*, 2H), 7.24-7.27 (m, H-6, H-6*, H-5", H-5"* , 4H), 6.69 (d, $J = 3.6$ Hz, H-3", H-3"* , 2H), 6.55-6.60 (m, H-3', H-3'* , H-5', H-5'* , 4H), 6.44-6.47 (m, H-2', H-2'* , H-6', H-6'* , 4H), 6.20 (dd, $J = 3.4$ Hz, 1.8 Hz, H-4", H-4"* , 2H), 5.81 (s, H-2, H-2*, CH, 2H), 3.63 (s, 2 x OCH₃, 6H), 3.55 (s, H-3, H-3*, 2H); $^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ_{C} 158.7 (C-4', C-4'*), 158.3 (C-1", C-1"*), 147.5 (C-2", C-2"*), 144.8 (C-9, C-9*), 144.6 (C-5", C-5"*), 135.3 (C-1', C-1'*), 130.7 (C-4, C-4*), 129.3 (C-7, C-7*), 125.6 (C-2', C-2'* , C-6', C-6'*), 125.4 (C-5, C-5*), 125.1 (C-6, C-6*), 118.1 (C-8, C-8*), 117.3 (C-3", C-3"*), 114.2 (C-3', C-3'* , C-5', C-5'*), 111.4 (C-4", C-4"*), 63.5 (C-2, C-2*), 57.2 (C-3, C-3*), 55.2 (2 x OCH₃); HRMS (+ESI) $[\text{M}+\text{H}]^+$: 637.2341, C₄₀H₃₃N₂O₆ requires 637.2333.

4. Conclusions

Although previous studies by our group have demonstrated the synthetic utility of benzophenone (an organocatalyst) as an effective additive for dramatically improving the yield of indolines (and suppressing bisindoline formation), the present study demonstrated that even in the absence of benzophenone, the amide structure can also under certain conditions discriminate between the indoline and bisindoline forms (enhancing the former and suppressing the latter). Stilbene **5** (with an *n*-butyramide moiety) will, on exposure to FeCl₃, give the corresponding indoline **14a** in 63% yield, compared to stilbene **6** (with an isobutyramide moiety) which yields indoline **15** in 29%. Previously undiscovered steric, conformational and stereoelectronic effects have been considered in this study involving eight stilbenes.

We would like to draw the reader's attention to some intriguing electronic effects. For example, stilbene **9** with an *ortho*-methoxy substituent dramatically shifts the electron density in the olefinic bond (see Table 1). The C(7) olefinic proton is now more deshielded than the C(8) proton. This in turn changes the position of the positive charge and unpaired electron (in the radical cation) compared to

stilbenes **11** and **12** with predictable consequences for the cyclization/dimerization. These transformations exploit FeCl₃ (an environmentally friendly oxidant) as the single electron transfer reagent [19-21]. Further developments will be reported in due course.

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References and Notes

1. Fuwa, H.; Sasaki, M. Synthesis of 2-substituted indoles and indolines via Suzuki-Miyaura coupling/5-*endo*-trig cyclization strategies. *J. Org. Chem.* **2009**, *74*, 212-221.
2. Prediger, I.; Weiss, T.; Reiser, O. Facile access to 2-arylindolines and 2-arylindoles by microwave-assisted tandem radical cyclization. *Synthesis* **2008**, *2008*, 2191-2198.
3. Anas, S.; Kagan, H.B. Routes toward enantiopure 2-substituted indolines: An overview. *Tetrahedron: Asymmetry* **2009**, *20*, 2193-2199.
4. Bailey, W.F.; Luderer, M.R.; Mealy, M.J. Preparation of differentially 1,3-disubstituted indolines by intramolecular carbolithiation. *Tetrahedron Lett.* **2003**, *44*, 5303-5305.
5. Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. Catalytic asymmetric hydrogenation of heteroaromatic compounds, indoles. *J. Am. Chem. Soc.* **2000**, *122*, 7614-7615.
6. Leroi, C.; Bertin, D.; Dufils, P.-E.; Gigmes, D.; Marque, S.; Tordo, P.; Couturier, J.-L.; Guerret, O.; Ciufolini, M.A. Alkoxyamine-mediated radical synthesis of indolinones and indolines. *Org. Lett.* **2003**, *5*, 4943-4945.
7. Muñiz, K. Advancing palladium-catalyzed C-N bond formation: Bisindoline construction from successive amide transfer to internal alkenes. *J. Am. Chem. Soc.* **2007**, *129*, 14542-14543.
8. Zhu, Q.; Huang, H.; Shi, D.; Shen, Z.; Xia, C. An efficient synthesis of chiral diamines with rigid backbones: Application in enantioselective michael addition of malonates to nitroalkenes. *Org. Lett.* **2009**, *11*, 4536-4539.
9. Movassaghi, M.; Schmidt, M.A. Concise total synthesis of (-)-calycanthine, (+)-chimonanthine, and (+)-folicanthine. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725-3728.
10. Thomas, N.F.; Velu, S.S.; Weber, J.-F.F.; Lee, K.C.; Hadi, A.H.A.; Richomme, P.; Rondeau, D.; Noorbach, I.; Awang, K. A tandem highly stereoselective FeCl₃-promoted synthesis of a bisindoline: Synthetic utility of radical cations in heterocyclic construction. *Tetrahedron* **2004**, *60*, 11733-11742.
11. Kam, T.-S.; Low, Y.-Y. We thank Prof. Kam and Mr Low (Dept. of Chem., University of Malaya) for crystal data of the bisindoline **4b**. A CIF file is included in the supplementary data submitted.
12. Thomas, N.F.; Kee, C.-H.; Ariffin, A.; Awang, K.; Weber, J.-F.F.; Lim, C.-G.; Mukhtar, M.R.; Hadi, A.H. The subtle co-catalytic intervention of benzophenone in radical cation mediated

- cyclization - an improved synthesis of 2-(3', 4'-dimethoxyphenyl) indoline. *Heterocycles* **2008**, *75*, 1097-1108.
13. Kee, C.H.; Ariffin, A.; Awang, K.; Takeya, K.; Morita, H.; Inayat Hussain, S.; Chan, K.M.; Wood, P.J.; Threadgill, M.D.; Lim, C.G.; *et al.* Challenges associated with the synthesis of unusual *o*-carboxamido stilbenes by the Heck protocol: Intriguing substituent effects, their toxicological and chemopreventive implications. *Org. Biomol. Chem.* **2010**, *8*, 5646-5660.
 14. Crich, D.; Shirai, M.; Brebion, F.; Rumthao, S. Enantioselective alkene radical cations reactions. *Tetrahedron* **2006**, *62*, 6501-6518.
 15. Ahmad, K.; Thomas, N.F.; Mukhtar, M.R.; Noorbachta, I.; Faizal Weber, J.-F.; Nafiah, M.A.; Velu, S.S.; Takeya, K.; Morita, H.; Lim, C.-G.; *et al.* A FeCl₃-promoted highly atropodistereoselective cascade reaction: Synthetic utility of radical cations in indolostilbene construction. *Tetrahedron* **2009**, *65*, 1504-1516.
 16. Anslyn, E.V.; Dougherty, D.A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, USA, 2006.
 17. Stewart, J. Optimization of parameters for semiempirical methods V: Modification of NDDO approximations and application to 70 elements. *J. Mol. Model.* **2007**, *13*, 1173-1213.
 18. Stewart, J. *Mopac 2009*; Stewart Computational Chemistry: Colorado Springs, CO, USA. <http://OpenMOPAC.net>
 19. Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. Iron-catalyzed reactions in organic synthesis. *Chem. Rev.* **2004**, *104*, 6217-6254.
 20. Díaz, D.D.; Miranda, P.O.; Padrón, J.I.; Martín, V.S. Recent uses of Iron (III) chloride in organic synthesis. *Curr. Org. Chem.* **2006**, *10*, 457-476.
 21. Sarhan, A.A.O.; Bolm, C. Iron (III) chloride in oxidative C-C coupling reactions. *Chem. Soc. Rev.* **2009**, *38*, 2730-2744.

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