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PAPER

Intramolecular palladium-catalysed enolate arylation of 2- and 3-iodoindole derivatives for the synthesis of β-carbolines, γ-carbolines, and pyrrolo[3,4-*b*]indoles†

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The palladium-catalysed intramolecular α-arylation of carbonyl compounds with amino-tethered 2- and 3-iodoindoles provides a useful methodology for the synthesis of indolo-*b*-fused nitrogen heterocycles. A variety of substituted tetrahydro β- and γ-carbolines, and pyrrolo[3,4-*b*]indoles, have been prepared by means of this palladium-catalysed annulation process.

Introduction

Indolo-*b*-fused nitrogen heterocycles are the structural basic units of a variety of natural products and synthetic biologically active compounds. Among *b*-annelated indoles, those containing five- and six-membered nitrogen heterocycles are of particular interest (Fig. 1). For example, the pyrido[3,4-*b*]indole framework (β-carboline) is central to a number of pharmaceutical targets[1] and is also present in diverse and more structurally complex natural products,[2] including for example the antihypertensive agents reserpine[3] and vincamine.[4] The pyrido[4,3-*b*]indole system (γ-carboline) has also been extensively studied, despite being present in only a few (very simple) naturally occurring products,[5] since γ-carbolines are precursors of the biologically active tetra- and hexahydro derivatives.[6] The pyrrolo[3,4-*b*]indole fragment also shows a broad spectrum of pharmacological activity.[7] Moreover, pyrrolo[3,4-*b*]indoles are valuable synthetic analogues of indole-2,3-quinodimethanes, which have been used in cycloaddition reactions leading to carbazoles, carbolines, and related systems.[8]

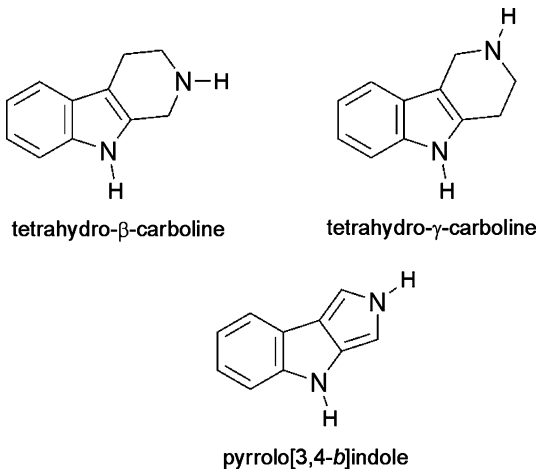

Fig. 1 Indolo-*b*-fused nitrogen heterocycles.

Given the importance of *b*-annelated indoles,[9] it is not surprising that many methods exist for their formation and that the development of new methodologies for their synthesis is a very active area of research. In particular, palladium-catalysed annulation processes have proven extremely useful for the construction of a wide variety of fused heterocyclic systems.[10]

As part of our ongoing program on the synthesis of natural products, we have been working in the development of efficient methodologies for the preparation of indolo-*b*-fused medium-sized nitrogen heterocycles.[11] We have also been studying the use of palladium-catalysed intramolecular coupling of amino-tethered aryl halides with enolates for the synthesis of heterocycles.[12] Continuing our research on both these aspects of synthetic chemistry, we were interested to see whether the palladium-catalysed intramolecular α-arylation of carbonyl compounds could be used for the preparation of diversely substituted indolo-*b*-fused nitrogen heterocycles.

During recent years, the palladium-catalysed arylation of enolate-type nucleophiles has received a great deal of attention.[13] In particular, the intramolecular version of these reactions[14–18] has found an increasing application in the synthesis of complex natural products.[19] Nevertheless, examples of these palladium-catalysed annulation processes involving haloindole substrates[20] are scarce and only feature the reactions of 4-haloindoles.[19f,19k,21]

Herein we report the application of the Pd-catalysed intramolecular α-arylation of carbonyl compounds to the construction of tetrahydro β- and γ-carbolines, and pyrrolo[3,4-*b*]indoles (Scheme 1).

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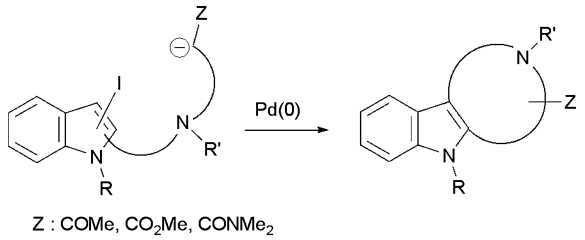


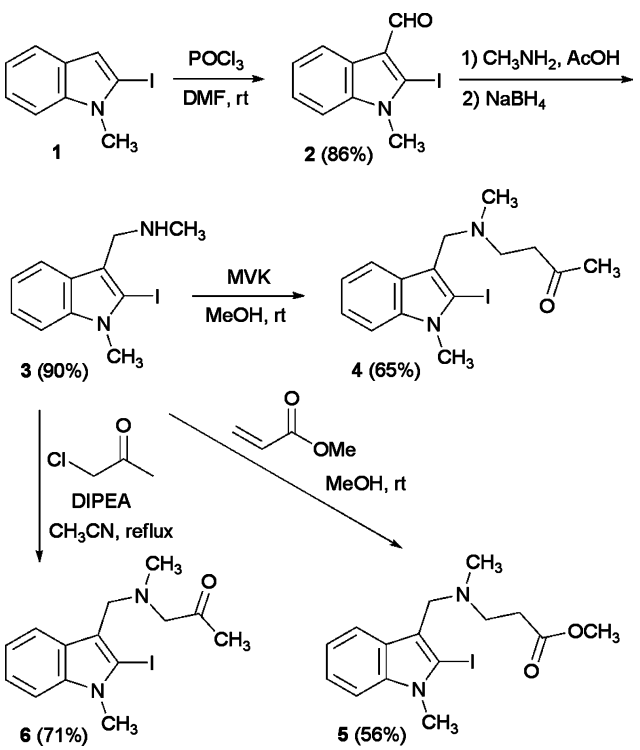
Scheme 1 Synthesis of indolo-*b*-fused nitrogen heterocycles by Pd(0)-catalysed enolate arylation.

Results and discussion

Synthesis of the starting materials

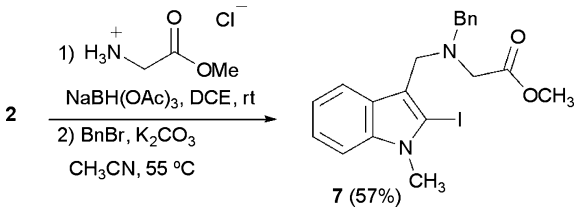
To establish the feasibility of our proposal, we focused on the palladium-catalysed reactions of 2- and 3-iodoindole substrates in which the length of the chain joining the indole nucleus and the carbonyl group, the position of the nitrogen in the tether, and the type of carbonyl compound were variously modified. To this end, 2-iodoindoles **4–7** and **21**, and 3-iodoindoles **11–14**, **17**, **18**, and **22** were chosen (Schemes 2–7).

These starting materials were efficiently prepared by standard methodologies. For the synthesis of ketones **4** and **6**, and esters **5** and **7** a fast formylation–reductive amination sequence starting from the known 2-iodoindole **1**[22] was used. Thus, formylation of **1** under Vilsmeier conditions afforded 3-formylindole **2**. Reductive amination of **2** with methylamine, followed by reaction of the resulting secondary amine **3** with methyl vinyl ketone, methyl acrylate or chloroacetone afforded β-aminoketone **4**, β-aminoester **5**, and α-aminoketone **6**, respectively (Scheme 2).



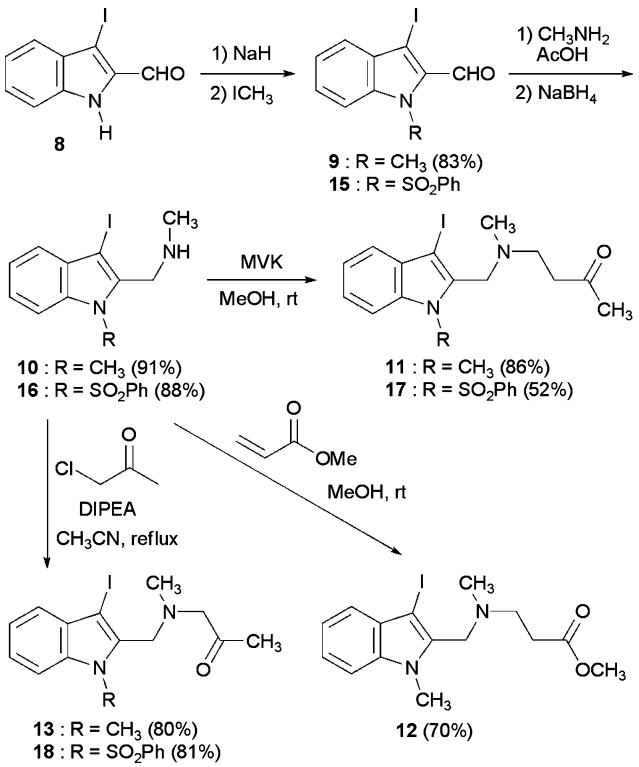
Scheme 2 Synthesis of 2-iodoindoles **4–6**.

On the other hand, reductive amination of **2** with glycine methyl ester, followed by reaction with benzyl bromide led to α-aminoester **7** (Scheme 3).

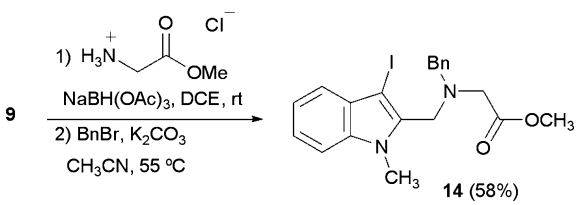


Scheme 3 Synthesis of 2-iodoindole **7**.

The 3-iodoindoles **11**, **12**, **13**, and **14** were prepared using similar reductive amination–alkylation sequences starting from 2-formyl-3-iodoindole **9**, which in turn was obtained by methylation of the known indole **8**[23](Schemes 4 and 5); and *N*-(phenylsulfonyl)indoles **17** and **18** were synthesized following the same sequences starting from the known 3-iodoindole **15** (Scheme 4).[23]



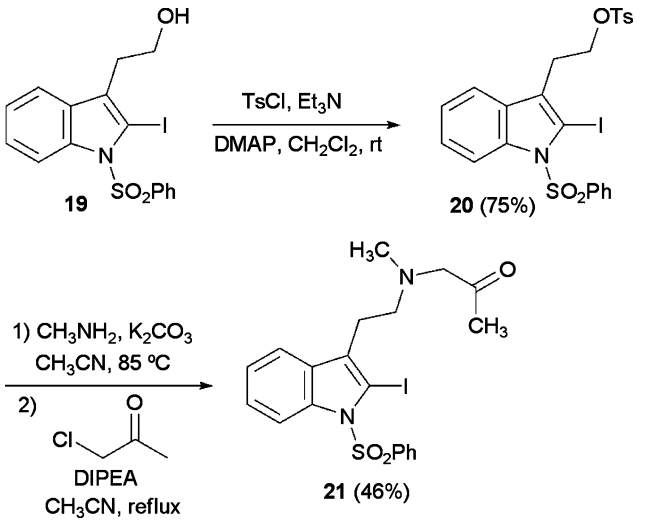
Scheme 4 Synthesis of 3-iodoindoles **11–13** and **17–18**.



Scheme 5 Synthesis of 3-iodoindole **14**.

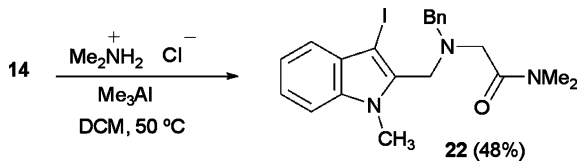
Treatment of tryptophol **19**[24] with *p*-toluenesulfonylchloride afforded sulfonic acid ester **20**, which on reaction with

methylamine, followed by alkylation of the resulting secondary amine with chloroacetone, led to tryptamine **21** (Scheme 6).



Scheme 6 Synthesis of 2-iodoindole **21**.

Finally, amide **22** was synthesized from ester **14** by reaction with the dimethylaluminium chloride dimethylamine complex[25] (Scheme 7).



Scheme 7 Synthesis of amide **22**.

α-Arylation reactions

The studies of the α-arylation reactions were initiated with β-aminoketones **4**, **11**, and **17**, and α-aminoketone **21**, from which the annulation would deliver tetrahydrocarboline derivatives. Several ligands, bases, and solvents were evaluated for the cyclization reaction, with the most significant results of these studies summarized in Table 1.

As we had previously observed in the reactions of (2-halobenzylamino) ketones,[12c] Cs_2CO_3 is, by far, the base of choice for the α-arylation processes of amino-tethered iodoindoles with ketones. When using K_3PO_4 as the base significant amounts of the starting material were usually recovered. Using ^{t}BuOK[12a] or PhOK[26] was not acceptable either, because only compounds arising from the retro-Michael degradation of the β-amino ketone moiety and hydrodehalogenation were isolated. Optimization of the solvent revealed that the reaction could be carried out in either toluene or THF, the latter usually giving inferior results.

From the plethora of ligands that have been used in Pd-catalysed α-arylation of carbonyl compounds,[13] we focused on six different commercially available phosphines (Fig. 2).

As can be seen in Table 1, among the β-amino ketones, the 2-iodoindole **4** afforded inferior results overall to the 3-iodoindoles **11** and **17**. The behaviour of **4** could be due to a combination of electronic factors together with the steric interaction between

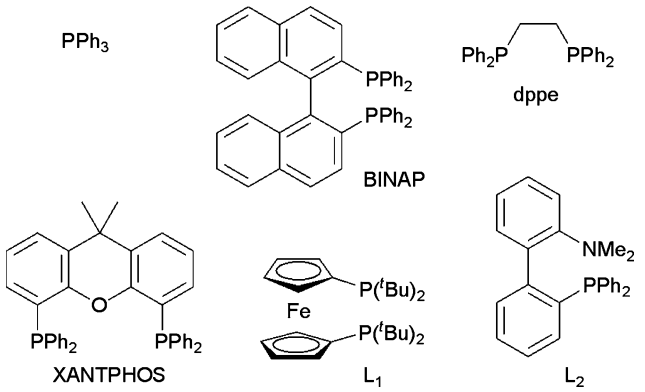


Fig. 2 Ligands used in the α-arylation reactions.

the methyl group at the indole N and the reactive point at C-2 of the indole. The best results with iodoindole **4** were obtained with Buchwald's monodentate ligand L_2 (Table 1, entry 6) and with diphosphine ligands with narrow natural bite angles (dppe and BINAP, Table 1, entries 3 and 2, respectively).

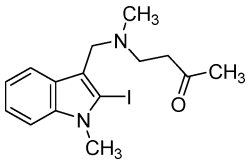
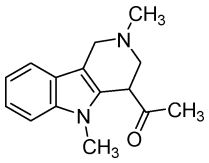
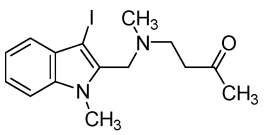
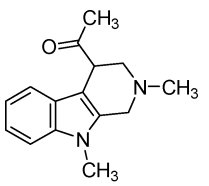
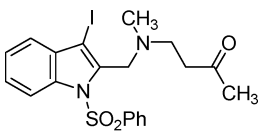
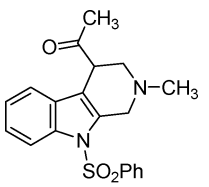
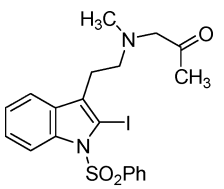
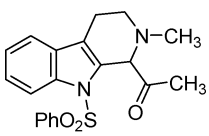
In contrast, in the cyclization reactions of 3-iodoindoles **11** and **17**, the best overall yields were obtained with the ferrocene-based ligand L_1, which has a wide bite angle (Table 1, entries 9 and 14). The only other ligand that allowed us to obtain both **24** and **25**, although in inferior yields, was BINAP (Table 1, entries 7 and 13). Interestingly, although the highest yield for the conversion of **17** to **25** was obtained using PPh_3 as the ligand (Table 1, entry 12), under the same reaction conditions **11** failed to undergo annulation and only afforded degradation compounds (not in the table).

In marked contrast to the cyclization of **4**, the ferrocene-based phosphine L_1 turned out to be the most effective ligand for the α-arylation of α-aminoketone **21** to provide tetrahydro-β-carboline **26** (Table 1, entry 17). Far worse results were obtained using the monodentate ligand L_2 (Table 1, entry 18), BINAP (Table 1, entry 16), or PPh_3 (Table 1, entry 15), while dppe in this instance resulted in the recovery of the starting material (not in the table).

The results of the ligand screening in the annulation reactions of **4**, **11**, **17**, and **21** show that the phosphine of choice for these processes is highly substrate-dependent and suggest that there is no correlation between the bite angle of the diphosphine ligand and the efficiency of the catalyst. The possibility of monodentate coordination for the diphosphines due to the ability of the distal amino group to chelate the palladium atom[12c,27,28] could account for the lack of bite-angle effects in these reactions.[29] On the other hand, the somewhat different behaviour between 2-iodoindoles **4** and **21** could be explained in part by the presence in the latter of the phenylsulfonyl group, which would also be able to weakly coordinate the initially formed indole–Pd(II) intermediate,[30] modifying both its stability and reactivity.

We extended the studies on the intramolecular α-arylation reaction of iodoindoles to β-amino esters **5** and **12** to prepare tetrahydrocarbolines **28** and **27**, respectively. Knowing that 3-iodoindoles behaved better in these cyclization reactions, we initiated the studies with β-amino ester **12**. As expected, the higher pK_a values of the esters made the α-arylation a more challenging task. In fact, major amounts of the starting material were recovered when the reaction was performed in the presence of all the ligands except BINAP. After some experimentation, the best results for the α-arylation of **12** to give β-carboline **27** were

Table 1 α-Arylation of aminoketones: synthesis of tetrahydrocarbolines[a]

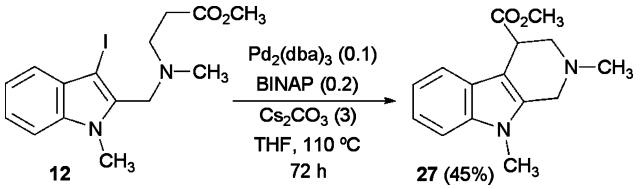
Entry	Aminoketone	Catalyst (equiv.)	Temp./time	Products (yield)[b]
				
1	**4**	$PdCl_2(PPh_3)_2$ (0.2)	110 °C/24 h[c]	**23** (21%)[d]
2	**4**	$Pd_2(dba)_3$ (0.05), BINAP (0.1)	110 °C/60 h	**23** (43%)[e]
3	**4**	$PdCl_2(PPh_3)_2$ (0.2), dppe (0.4)	110 °C/72 h[c]	**23** (45%)
4	**4**	$Pd_2(dba)_3$ (0.05), L_1 (0.1)	90 °C/24 h	**23** (18%)[d]
5	**4**	$Pd_2(dba)_3$ (0.05), xantphos (0.1)	90 °C/24 h	**23** (17%)[d]
6	**4**	$Pd_2(dba)_3$ (0.05), L_2 (0.1)	110 °C/72 h	**23** (51%)
				
7	**11**	$Pd_2(dba)_3$ (0.05), BINAP (0.1)	110 °C/48 h	**24** (49%)[f]
8	**11**	$Pd_2(dba)_3$ (0.05), dppe (0.1)	110 °C/24 h	**24** (40%)[g]
9	**11**	$Pd_2(dba)_3$ (0.05), L_1 (0.1)	90 °C/24 h	**24** (60%)
10	**11**	$Pd_2(dba)_3$ (0.05), xantphos (0.1)	90 °C/24 h	**24** (41%)
11	**11**	$Pd_2(dba)_3$ (0.05), L_2 (0.1)	110 °C/24 h	**24** (43%)[h]
				
12	**17**	$Pd(PPh_3)_4$ (0.1)	110 °C/24 h	**25** (65%)
13	**17**	$Pd_2(dba)_3$ (0.05), BINAP (0.1)	110 °C/48 h	**25** (40%)[i]
14	**17**	$Pd_2(dba)_3$ (0.05), L_1 (0.1)	90 °C/24 h	**25** (59%)
				
15	**21**	$Pd(PPh_3)_4$ (0.1)	110 °C/48 h[c]	**26** (30%)
16	**21**	$Pd_2(dba)_3$ (0.1), BINAP (0.2)	110 °C/48 h	**26** (18%)
17	**21**	$Pd_2(dba)_3$ (0.05), L_1 (0.1)	90 °C/30 h	**26** (70%)
18	**21**	$Pd_2(dba)_3$ (0.1), L_2 (0.2)	110 °C/48 h	**26** (47%)

[a] α-Arylation reactions were run with the iodoindole (0.15–0.20 mmol), the catalyst, and Cs_2CO_3 (3 equiv.) in toluene in a sealed tube. [b] Yield refers to pure isolated products. [c] THF was used as the solvent. [d] 4-Acetyl-4-hydroxy-2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole was also isolated (5–10%). [e] When using K_3PO_4 (3 equiv.) as the base a 9 : 1 mixture of **4** and **23** was obtained. [f] When using THF as the solvent **24** was obtained in 35% yield. [g] When using THF as the solvent a 9 : 1 mixture of **11** and **24** was obtained. [h] When using THF as the solvent a 1 : 1 mixture of **11** and **24** was obtained. [i] Secondary amine **16** was also isolated (20%).

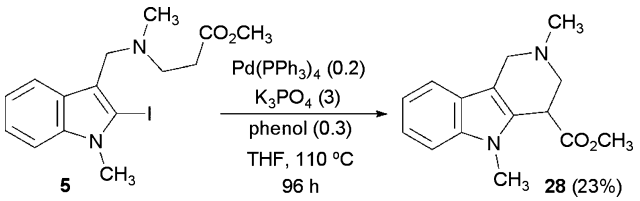
obtained using BINAP and Cs_2CO_3 as the base in THF at 110 °C (Scheme 8).

However, the application of these reaction conditions to 2-iodoindole **5** also resulted in the recovery of the starting material. The α-arylation was finally accomplished, although in a modest 23% yield, by a lengthy treatment of **5** with $Pd(PPh_3)_4$ and K_3PO_4 together with a catalytic amount of phenol[12e,31] in THF at 110 °C (Scheme 9).

The reluctance of esters **5** and **12**, which were mainly recovered unchanged, to undergo the α-arylation reaction could be due to a combination of the high stability of the initially formed Pd(II) chelates[30] together with the lower acidity of the ester, which would



Scheme 8 α-Arylation reaction of ester **12**.



Scheme 9 α-Arylation reaction of ester **5**.

make these intermediates unreactive under the reaction conditions and would result in the removal of the Pd catalyst from the catalytic cycle.

On the other hand, it should be noted that the moderate efficiency of the α-arylation reactions of the β-amino ketone and β-amino ester substrates is partially a consequence of their marked tendency to undergo retro-aza-Michael fragmentation, which result in the formation of diverse degradation compounds (see for example Table 1, entry 13).

At this point we turned our attention to the α-arylation reactions of α-amino carbonyl derivatives to provide pyrrolo[3,4-*b*]indoles (Table 2).[32] We have previously described how isoindoles can be directly obtained by sequential palladium-catalysed arylation–dehydrogenation of α-(2-iodobenzylamino) ketones.[12c] We have also reported that isoindoles and isoindolines can be selectively synthesized by means of palladium-catalysed arylation of α-amino esters.[12h]

The use of $Pd(PPh_3)_4$ as the catalyst and Cs_2CO_3 as the base in THF, a combination that is effective for the preparation of isoindoles from α-amino ketones,[12c] was found to be less efficient for the present α-arylation–dehydrogenation process. For example, treatment of **6** under these reaction conditions resulted in the recovery of significant amounts of the starting material together with minor amounts of **29** (not in the table). A similar result was obtained when dppe was used as the ligand instead of PPh_3 (not in the table). Complete conversion of the starting material was observed when using BINAP as the ligand, and pyrrolo[3,4-*b*]indole **29** was obtained in 35% yield (Table 2, entry 1). The use of $Pd(PPh_3)_4$ in the presence of K_3PO_4 together with a catalytic amount of phenol in DMF also resulted in the total consumption of the starting material, but the isolated yield of **29** was reduced to 25% (Table 2, entry 2).

Interestingly, the use of both catalysts Pd-BINAP (Table 2, entry 3) and $Pd(PPh_3)_4$ (Table 2, entry 4) for the reaction of 3-iodoindole **13** resulted in the formation of nearly equimolar mixtures of the pyrrolo[3,4-*b*]indole **30** and alcohol **31**, the latter resulting from the addition of the arylpalladium intermediate to the ketone carbonyl. While we were unable to increase the ratio of the arylation product, we observed that when using dppe as the ligand the nucleophilic addition to the carbonyl group was the only apparent reaction, alcohol **31** being isolated in 48% yield (Table 2, entry 5). We have previously observed the competition between α-arylation and the nucleophilic attack on the carbonyl in the Pd-catalysed reactions of β-(2-haloanilino) ketones.[12c,33] Computational studies have shown that the delocalisation of the LP in the π-system of the aniline increases the nucleophilicity of the reactive arylic carbon atom, favouring the attack on the carbonyl group.[34] As a similar delocalisation operates in **13**, we realized that by significantly decreasing the nucleophilicity of the indole C-3 position we could favour the α-arylation process instead. In fact, the nucleophilic addition to the ketone carbonyl was not observed in any of the Pd-catalysed reactions of *N*-phenylsulfonylindole **18**. Performing the α-arylation of **18** using BINAP as the ligand afforded the desired pyrrolo[3,4-*b*]indole **32** in 58% yield (Table 2, entry 6).[35] PPh_3 and dppe were less effective for the present α-arylation–dehydrogenation reaction (Table 2, entries 7 and 8).

The Pd-catalysed cyclization was extended to α-aminoesters **7** and **14**, and carboxamide **22** (Table 3). Knowing the efficiency of $Pd(PPh_3)_4$ for the synthesis of both isoindoles and isoindolines starting from α-(2-iodobenzylamino) esters,[12h] we decided to initially centre our studies on the ligand PPh_3. As shown in Table 3, the α-arylation process starting from α-amino esters allowed either the pyrrolo[3,4-*b*]indoles or the corresponding dihydro derivatives to be selectively obtained by changing the reaction conditions. Thus, while treatment of **7** with $Pd(PPh_3)_4$ and K_3PO_4 together with a catalytic amount of phenol in DMF afforded the product resulting from the α-arylation–dehydrogenation process **33** (Table 3, entry 1), the use of $Pd(PPh_3)_4$ in combination with Cs_2CO_3 as the base in THF gave the dihydro derivative **34** (Table 3, entry 2). The use of BINAP instead of PPh_3 under the latter reaction conditions afforded a complex mixture in which **34** was again the main product (not in the table).

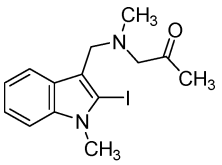
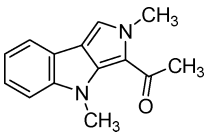
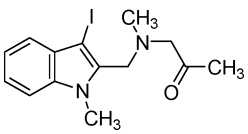
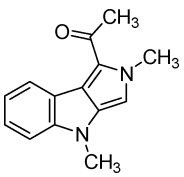
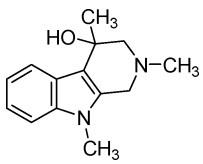
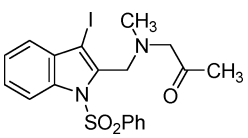
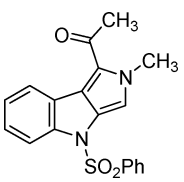
Similar results were obtained in the Pd-catalysed cyclization of 3-iodoindole **14**, which afforded the pyrrolo[3,4-*b*]indole **35** when using the K_3PO_4/phenol couple in DMF (Table 3, entry 3) and the dihydro derivative **36** when the reaction was performed in the presence of Cs_2CO_3 in THF (Table 3, entry 4). Whereas BINAP was equally effective as PPh_3 for the preparation of **36** (Table 3, entry 5), the other ligands gave very low yields (not in the table). The instability and high tendency to undergo aerial oxidation of pyrrolo[3,4-*b*]indole derivatives, which hampers their isolation,[35] could account for the moderate-to-low yields obtained in the α-arylation of α-amino carbonyl substrates.

Finally, the α-arylation of carboxamide **22** was explored. In contrast to the reactions of α-aminoesters, treatment of **22** with $Pd(PPh_3)_4$ in the presence of K_3PO_4 and phenol in DMF afforded the dihydro derivative **37** in 58% yield, with the product arising from the subsequent aromatization reaction being undetected (Table 3, entry 7). The same result was obtained, although in inferior yields, when the reaction was conducted using K_3PO_4 as the base in THF in the presence of the ligands PPh_3, BINAP or the monophosphine L_2 (Table 3, entries 6, 8 and 9).

Conclusions

The present paper reports our studies on the implementation of the palladium-catalysed intramolecular arylation of enolate-type

Table 2 α-Arylation of α-aminoketones: synthesis of pyrrolo[3,4-*b*]indoles

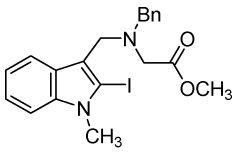
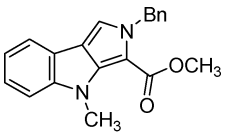
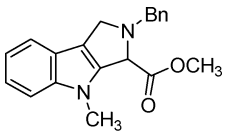
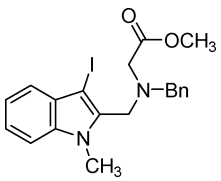
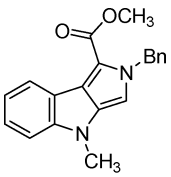
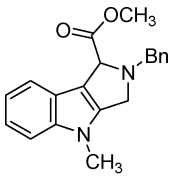
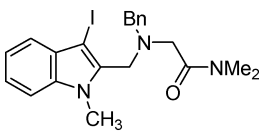
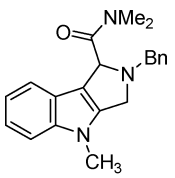
Entry	α-Aminoketone	Catalyst (equiv.)	Base (equiv.); additive (equiv.)	Solvent	*T*/time	Products (yield)[a]	
							
1	**6**	$Pd_2(dba)_3$ (0.05); BINAP (0.1)	Cs_2CO_3 (3)	Toluene[b]	110 °C/72 h	**29** (35%)	
2	**6**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3); phenol (0.3)	DMF	90 °C/23 h	**29** (25%)	
							
3	**13**	$Pd_2(dba)_3$ (0.05); BINAP (0.1)	Cs_2CO_3 (3)	Toluene[b]	110 °C/72 h	**30** (31%)	**31** (35%)
4	**13**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3); phenol (0.3)	DMF	90 °C/24 h	**30** (24%)	**31** (30%)
5	**13**	$Pd(OAc)_2$ (0.2); dppe (0.25)	Cs_2CO_3 (3)	Toluene[b]	110 °C/72 h		**31** (48%)
							
6	**18**	$Pd_2(dba)_3$ (0.05); BINAP (0.1)	Cs_2CO_3 (3)	Toluene[b]	110 °C/72 h	**32** (58%)	
7	**18**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3); phenol (0.3)	DMF	90 °C/24 h	**32** (30%)	
8	**18**	$Pd(OAc)_2$ (0.2); dppe (0.25)	Cs_2CO_3 (3)	Toluene[b]	110 °C/72 h	**32** (15%)	

[a] Yield refers to pure isolated products. [b] Reactions were run in a sealed tube.

nucleophiles in the synthesis of indolo-*b*-fused nitrogen heterocycles. The use of enolates derived from ketones, esters, and amides has been explored for the preparation of annelated 5- and 6-membered azaheterocycles. By means of this methodology, diversely substituted pyrido[3,4-*b*]indoles (β-carbolines), pyrido[4,3-*b*]indoles (γ-carbolines), and pyrrolo[3,4-*b*]indoles were prepared. The results obtained in the annulation reactions show that the phosphine of choice for these processes is highly substrate-dependent. A lack of bite-angle effects, probably due to the coordination ability of the tether amino group, was also revealed. On the whole, BINAP proved to be the most versatile ligand, although it did not always give the highest yield. Thus, the use of BINAP produced acceptable results (40–58% yield) in the α-arylation reactions of all substrates except 2-iodoindole **5**, which was recovered unchanged, and 2-iodoindoles **7** and **21**, which in the presence of this ligand performed the annulation in very low yields.

It should be noted that the obligatory use of weak bases (Cs_2CO_3 and K_3PO_4) in the above α-arylation reactions, which results in a low concentration of the enolate in the reaction mixture, could be another important factor in understanding the low efficiency of some of the reactions. In this context, among the carbonyl moieties, annulation reactions of β-amino ester substrates proved especially troublesome probably due to their higher pK_a values. The reactions of α-amino carbonyl compounds gave different results depending on the nature of the carbonyl group. Thus, starting from α-amino ketones, pyrrolo[3,4-*b*]indoles were obtained by means of an α-arylation–dehydrogenation process, while the α-arylation of amide **22** exclusively afforded the corresponding dihydro derivative. In contrast, the annulation processes of α-amino esters allowed either the fully aromatic compounds or their dihydro derivatives to be selectively obtained depending on the reaction conditions. Further experimentation will be performed

Table 3 α-Arylation of α-aminoesters **7** and **14**, and amide **22**: synthesis of pyrrolo[3,4-*b*]indoles

Entry	Starting material	Catalyst (equiv.)	Base (equiv.) additive (equiv.)	Solvent	Temp./time	Products (yield)[a]	
							
1	**7**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3); phenol (0.3)	DMF	90 °C/24 h	**33** (50%)	
2	**7**	$Pd(PPh_3)_4$ (0.1)	Cs_2CO_3 (3)	THF[b]	110 °C/72 h		**34** (31%)[c]
							
3	**14**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3); phenol (0.3)	DMF	90 °C/24 h	**35** (60%)	
4	**14**	$Pd(PPh_3)_4$ (0.1)	Cs_2CO_3 (3)	THF[b]	110 °C/72 h		**36** (56%)
5	**14**	$Pd_2(dba)_3$ (0.1); BINAP (0.2)	Cs_2CO_3 (3)	THF[b]	110 °C/48 h		**36** (50%)
							
6	**22**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3)	THF[b]	110 °C/48 h		**37** (54%)
7	**22**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3); phenol (0.3)	DMF	90 °C/24 h		**37** (58%)
8	**22**	$Pd_2(dba)_3$ (0.1); BINAP (0.2)	K_3PO_4 (3)	THF[b]	110 °C/42 h		**37** (50%)
9	**22**	$Pd_2(dba)_3$ (0.1); L_2 (0.2)	K_3PO_4 (3)	THF[b]	110 °C/48 h		**37** (40%)

[a] Yield refers to pure isolated products. [b] Reactions were run in a sealed tube. [c] ^1H NMR analysis of the crude reaction mixture gave **34** as the main product together with trace amounts of **33**. However, after column chromatography **33** was isolated in 15% yield.

in order to expand the present methodology to the synthesis of other indolo-fused nitrogen heterocycles.

Experimental

General

All commercially available reagents were used without further purification. Solvents were dried prior to use according to standard methods. Drying of organic extracts during workup of reactions was performed over anhydrous $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Thin-layer chromatography was carried out using commercial aluminium-backed silica gel plates and the spots were located with UV light (254 nm), iodoplatinate reagent or 1% aqueous $KMnO_4$. Flash chromatography was carried out on SiO_2 (silica gel 60, 230–400 mesh ASTM). Unless otherwise noted, ^1H- and ^{13}C NMR spectra were recorded in $CDCl_3$ solution, using Me_4Si as the internal standard, with a Varian Gemini 300 or a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. IR spectra were recorded on a Nicolet Avatar-320 Fourier transform IR spectrometer and data are reported in reciprocal centimetres (cm^{-1}).

General methods for the Pd-catalysed reactions

Representative procedure for the Pd-catalysed reactions in a sealed tube (Table 1, entry 6). A mixture of ketone **4** (75 mg, 0.20 mmol), Cs_2CO_3 (195 mg, 0.60 mmol), $Pd_2(dba)_3$ (9 mg, 0.01 mmol), and L_2 (8 mg, 0.02 mmol) in toluene (8 mL) was stirred at 110 °C in a sealed tube for 72 h. The reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (from CH_2Cl_2 to CH_2Cl_2–MeOH 1%) to give **23** as a yellow oil (25 mg, 51%).

Representative procedure for the Pd-catalysed reactions in DMF (Table 3, entry 3). A mixture of ester **14** (75 mg, 0.17 mmol),

K_3PO_4 (108 mg, 0.51 mmol), phenol (5 mg, 0.051 mmol), and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) in DMF (3 mL) was stirred at 90 °C for 24 h. The reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with 1 N NaOH solution and brine, dried, and concentrated. The residue was purified by chromatography (from hexanes to 9 : 1 hexanes-EtOAc) to give **35** as an orange oil (32 mg, 60%).

4-Acetyl-2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]-indole (23). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.17 (s, 3H), 2.51 (s, 3H), 2.82 (dd, J = 11.6 and 4.8 Hz, 1H), 3.14 (dd, J = 11.6 and 2.8 Hz, 1H), 3.40 (d, J = 13.6 Hz, 1H), 3.57 (s, 3H), 3.70 (broad s, 1H), 4.02 (d, J = 13.6 Hz, 1H), 7.11 (dd, J = 8 and 7.2 Hz, 1H), 7.22 (dd, J = 8 and 7.2 Hz, 1H), 7.29 (d, J = 8 Hz, 1H), 7.47 (d, J = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.8 (CH_3), 29.5 (CH_3), 45.7 (CH_3), 48.8 (CH), 51.6 (CH_2), 56.1 (CH_2), 109.1 (CH), 109.8 (C), 118.1 (CH), 119.2 (CH), 121.6 (CH), 125.1 (C), 131.2 (C), 137.4 (C), 209.9 (C). IR (NaCl) ν 2938, 2788, 1708, 1666, 1612, 1469, 1361, 1319, 1247, 1133, 742 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32).1/2H_2O: C, 71.69; H, 7.62; N, 11.15. Found: C, 71.58; H, 7.56; N, 10.85.

4-Acetyl-2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]-indole (24). Purification by flash chromatography (from CH_2Cl_2 to 1% CH_2Cl_2–MeOH) gave a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3H), 2.54 (s, 3H), 2.75 (dd, J = 11.6 and 4.8 Hz, 1H), 3.13 (dd, J = 11.6 and 4.4 Hz, 1H), 3.45 (dd, J = 14.4 and 1.2 Hz, 1H), 3.64 (s, 3H), 3.78 (dd, J = 4.8 and 4.4 Hz, 1H), 3.89 (d, J = 14.4 Hz, 1H), 7.11 (ddd, J = 8, 7.2, and 0.8 Hz, 1H), 7.21 (ddd, J = 8, 7.2, and 1.2 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 7.41 (d, J = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.5 (CH_3), 29.3 (CH_3), 45.7 (CH_3), 47.7 (CH), 51.4 (CH_2), 55.3 (CH_2), 105.3 (C), 108.9 (CH), 118.2 (CH), 119.5 (CH), 121.2 (CH), 126.3 (C), 134.8 (C), 137.2 (C), 211.4 (C). IR (NaCl) ν 2940, 2786, 1702, 1651, 1612, 1470, 1355, 1324, 1242, 1188, 1138, 747 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{15}H_{19}N_2O$ 243.1492, found 243.1499.

4-Acetyl-2-methyl-9-phenylsulfonyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (25). Purification by flash chromatography (from CH_2Cl_2 to 1% CH_2Cl_2–MeOH) gave a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (s, 3H), 2.52 (s, 3H), 2.72 (dd, J = 11.7 and 4.8 Hz, 1H), 3.08 (dd, J = 11.7 and 3.9 Hz, 1H), 3.66 (dd, J = 4.8 and 3.9 Hz, 1H), 3.67 (d, J = 16.5 Hz, 1H), 4.26 (d, J = 16.5 Hz, 1H), 7.21–7.35 (m, 3H), 7.43 (m, 2H), 7.54 (m, 1H), 7.79 (m, 2H), 8.13 (d, J = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.4 (CH_3), 45.4 (CH_3), 47.5 (CH), 53.2 (CH_2), 54.5 (CH_2), 114.4 (CH), 115.2 (C), 118.6 (CH), 123.9 (CH), 124.6 (CH), 126.3 (2 CH), 129.0 (C), 129.3 (2 CH), 133.9 (CH), 134.5 (C), 136.3 (C), 138.4 (C), 209.3 (C). IR (NaCl) ν 2944, 2796, 1707, 1606, 1451, 1380, 1226, 1174, 1119, 1089, 752 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{20}H_{21}N_2O_3S$ 369.1267, found 369.1265.

1-Acetyl-2-methyl-9-phenylsulfonyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (26). Purification by flash chromatography (from CH_2Cl_2 to 1% CH_2Cl_2–MeOH) gave a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 2.50 (m, 1H), 2.57 (s, 3H), 2.80–3.12 (m, 3H), 4.86 (s, 1H), 7.19–7.25 (m, 3H), 7.38–7.44 (m, 3H), 7.51 (m, 1H), 7.77–8.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.6 (CH_2), 28.0 (CH_3), 42.4 (CH_3), 44.9 (CH_2), 67.9 (CH), 113.9 (CH), 118.2 (C), 118.7 (CH), 123.3 (CH), 124.6 (CH), 126.9 (2 CH), 129.1 (2 CH), 129.5 (C), 130.6 (C), 133.6 (CH), 135.8 (C), 138.6 (C), 204.2 (C). IR (NaCl) ν 2937, 2798, 1720, 1642, 1450, 1365, 1232, 1170, 1148, 1088, 752 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{20}H_{21}N_2O_3S$ 369.1267, found 369.1270.

Methyl 2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxylate (27). Purification by flash chromatography (from CH_2Cl_2 to 1% CH_2Cl_2–MeOH) gave a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.57 (s, 3H), 2.82 (dd, J = 11.7 and 4.8 Hz, 1H), 3.24 (dd, J = 11.7 and 5.1 Hz, 1H), 3.48 (d, J = 14.7 Hz, 1H), 3.61 (s, 3H), 3.73 (s, 3H), 3.83 (d, J = 14.7 Hz, 1H), 3.96 (dd, J = 5.1 and 4.8 Hz, 1H), 7.09 (ddd, J = 8.1, 7.2, and 1.2 Hz, 1H), 7.18 (ddd, J = 8.1, 7.2, and 1.2 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 29.2 (CH_3), 39.4 (CH), 45.7 (CH_3), 51.4 (CH_2), 52.0 (CH_3), 55.1 (CH_2), 104.3 (C), 108.8 (CH), 118.8 (CH), 119.3 (CH), 121.0 (CH), 126.4 (C), 134.5 (C), 137.2 (C), 173.9 (C). IR (NaCl) ν 2949, 2788, 1732, 1652, 1613, 1470, 1437, 1380, 1325, 1248, 1194, 1059, 749 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{15}H_{19}N_2O_2$ 259.1441, found 259.1443.

Methyl 2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-4-carboxylate (28). Purification by flash chromatography (from CH_2Cl_2 to 1% CH_2Cl_2–MeOH) gave a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.54 (s, 3H), 2.79 (dd, J = 11.7 and 4.2 Hz, 1H), 3.41 (dd, J = 11.7 and 3.9 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.63 (s, 3H), 3.74 (s, 3H), 3.82 (broad s, 1H), 3.98 (d, J = 13.8 Hz, 1H), 7.08 (ddd, J = 8.1, 7.2, and 1.2 Hz, 1H), 7.20 (ddd, J = 8.1, 7.2, and 1.2 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 29.7 (CH_3), 40.3 (CH), 45.7 (CH_3), 51.8 (CH_2), 52.5 (CH_3), 55.9 (CH_2), 108.9 (CH), 109.6 (C), 118.1 (CH), 118.9 (CH), 121.4 (CH), 124.8 (C), 130.0 (C), 137.4 (C), 172.3 (C). IR (NaCl) ν 2944, 2789, 1732, 1616, 1471, 1388, 1318, 1250, 1136, 1052, 993, 741 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{15}H_{19}N_2O_2$ 259.1441, found 259.1442.

3-Acetyl-2,4-dimethyl-2,4-dihydropyrrolo[3,4-*b*]indole (29). Purification by flash chromatography (from CH_2Cl_2 to 1% CH_2Cl_2–MeOH) gave an orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.65 (s, 3H), 4.01 (s, 3H), 4.07 (s, 3H), 7.08 (s, 1H), 7.12 (ddd, J = 8.5, 7.5, and 1 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.32 (td, J = 7.5 and 1 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 30.5 (CH_3), 34.1 (CH_3), 39.8 (CH_3), 109.4 (CH), 114.9 (C), 119.4 (CH), 119.6 (C), 119.8 (CH), 120.1 (CH), 123.9 (CH), 128.4 (C), 128.9 (C), 146.4 (C), 184.7 (C). ESI-HRMS [M+H]$^+$ calcd for $C_{14}H_{15}N_2O$ 227.1179, found 227.1179.

1-Acetyl-2,4-dimethyl-2,4-dihydropyrrolo[3,4-*b*]indole (30). Purification by flash chromatography (Et_2O and 1% Et_2O-diethylamine) gave an orange oil (first product on elution). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.87 (s, 3H), 3.69 (s, 3H), 4.16 (3H), 6.71 (s, 1H), 7.15 (ddd, J = 8.1, 7.2, and 1.2 Hz, 1H), 7.27 (d, J = 7.2 Hz, 1H), 7.40 (td, J = 7.2 and 1.2 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H). ^{13}C NMR spectrum could not be obtained because **30** decomposed during the experiment.

2,4,9-Trimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-4-ol (31). Purification by flash chromatography (Et_2O and 1% Et_2O-diethylamine) gave a yellow oil (second product on elution). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.73 (s, 3H), 2.47 (d, J = 11.4 Hz, 1H), 2.54 (s, 3H), 2.85 (d, J = 11.4 Hz, 1H), 3.20 (d, J = 14.4 Hz, 1H), 3.48 (s, 3H), 3.69 (d, J = 14.4 Hz, 1H), 7.11 (ddd, J = 7.8, 6.9, and

1.2 Hz, 1H), 7.19 (ddd, J = 8.1, 6.9, and 1.2 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.2 (CH_3), 29.1 (CH_3), 45.9 (CH_3), 51.8 (CH_2), 68.2 (CH_2), 77.2 (C), 108.8 (CH), 113.3 (C), 119.4 (CH), 119.8 (CH), 121.0 (CH), 124.8 (C), 134.6 (C), 137.2 (C). IR (NaCl) ν 3342, 2939, 2793, 1470, 1377, 1323, 1101, 742 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{14}H_{19}N_2O$ 231.1492, found 231.1492.

1-Acetyl-2-methyl-4-phenylsulfonyl-2,4-dihydropyrrolo[3,4-*b*]indole (32). Purification by flash chromatography (CH_2Cl_2) gave an orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.73 (s, 3H), 4.11 (3H), 7.23 (s, 1H), 7.26–7.42 (m, 4H), 7.47 (m, 1H), 7.78 (m, 2H), 7.95 (d, J = 8 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 31.0 (CH_3), 39.5 (CH_3), 113.4 (CH), 115.0 (CH), 120.9 (C), 121.5 (C), 122.6 (CH), 123.7 (C), 124.0 (CH), 126.3 (CH), 126.6 (2 CH), 129.0 (2 CH), 129.8 (C), 133.8 (CH), 136.9 (C), 142.4 (C), 187.6 (C). IR (NaCl) ν 2956, 1648, 1494, 1466, 1369, 1294, 1219, 1176, 1150, 1090, 954, 756 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{19}H_{17}N_2O_3S$ 353.0954, found 353.0955.

Methyl 2-benzyl-4-methyl-2,4-dihydropyrrolo[3,4-*b*]indole-3-carboxylate (33). Purification by flash chromatography (from hexanes to 5% hexanes-EtOAc) gave an orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 3H), 3.99 (s, 3H), 5.69 (s, 2H), 7.07–7.14 (m, 3H), 7.20–7.35 (m, 6H), 7.70 (d, J = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 32.1 (CH_3), 50.5 (CH_3), 54.0 (CH_2), 100.9 (C), 109.0 (CH), 115.3 (C), 118.6 (CH), 119.0 (CH), 119.4 (C), 119.9 (CH), 124.0 (CH), 126.5 (2 CH), 127.3 (CH), 128.6 (2 CH), 138.7 (C), 141.6 (C), 146.3 (C), 161.1 (C). IR (NaCl) ν 2946, 1684, 1588, 1448, 1315, 1229, 1198, 1093, 741 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{20}H_{19}N_2O_2$ 319.1441, found 319.1430.

Methyl 2-benzyl-4-methyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole3-carboxylate (34). Purification by flash chromatography (CH_2Cl_2) gave a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 3H), 3.71 (3H), 3.97 (dd, J = 11.4 and 2.4 Hz, 1H), 4.11 (d, J = 13.2 Hz, 1H), 4.22 (d, J = 13.2 Hz, 1H), 4.35 (dd, J = 11.4 and 3.9 Hz, 1H), 4.85 (dd, J = 3.9 and 2.4 Hz, 1H), 7.08 (m, 1H), 7.19 (m, 1H), 7.25–7.45 (m, 7H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 30.9 (CH_3), 52.2 (CH_3), 52.9 (CH_2), 58.4 (CH_2), 65.1 (CH), 109.7 (CH), 116.4 (C), 119.1 (CH), 119.6 (CH), 121.2 (CH), 122.5 (C), 127.2 (CH), 128.4 (2 CH), 128.8 (2 CH), 138.7 (C), 139.0 (C), 141.4 (C), 171.9 (C). IR (NaCl) ν 2948, 2805, 1736, 1685, 1588, 1466, 1315, 1259, 1197, 1130, 1094, 740 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{20}H_{21}N_2O_2$ 321.1598, found 321.1599.

Methyl 2-benzyl-4-methyl-2,4-dihydropyrrolo[3,4-*b*]indole-1-carboxylate (35). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.66 (s, 3H), 4.01 (s, 3H), 5.82 (s, 2H), 6.75 (s, 1H), 7.12–7.17 (m, 3H), 7.20–7.33 (m, 4H), 7.39 (m, 1H), 8.22 (d, J = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 31.0 (CH_3), 51.0 (CH_3), 52.8 (CH_2), 105.0 (CH), 108.2 (CH), 109.6 (C), 118.2 (CH), 119.8 (C), 120.9 (C), 123.1 (CH), 125.2 (CH), 126.7 (2 CH), 127.4 (CH), 128.6 (2 CH), 135.8 (C), 138.7 (C), 146.4 (C), 161.7 (C). IR (NaCl) ν 2946, 1693, 1625, 1594, 1516, 1495, 1474, 1449, 1380, 1337, 1297, 1194, 1146, 1096, 745 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{20}H_{19}N_2O_2$ 319.1441, found 319.1436.

Methyl 2-benzyl-4-methyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]-indole-1-carboxylate (36). Purification by flash chromatography (from CH_2Cl_2 to 1% CH_2Cl_2–MeOH) gave a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.62 (s, 3H), 3.76 (3H), 3.89 (dd, J = 12.8 and 3.2 Hz, 1H), 4.02 (d, J = 13.6 Hz, 1H), 4.28 (d, J = 13.6 Hz, 1H), 4.29 (dd, J = 12.8 and 4 Hz, 1H), 4.92 (dd, J = 4 and 3.2 Hz, 1H), 7.10 (m, 1H), 7.17 (m, 1H), 7.24–7.38 (m, 4H), 7.46 (m, 2H), 7.52 (d, J = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 31.2 (CH_3), 51.2 (CH_2), 51.9 (CH_3), 58.7 (CH_2), 66.3 (CH), 109.6 (CH), 112.3 (C), 118.7 (CH), 119.8 (CH), 120.8 (CH), 122.8 (C), 127.3 (CH), 128.4 (2 CH), 128.9 (2 CH), 138.8 (C), 141.0 (C), 142.9 (C), 172.9 (C). IR (NaCl) ν 2946, 2800, 1748, 1694, 1593, 1494, 1457, 1370, 1320, 1265, 1197, 1169, 1131, 1073, 741 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{20}H_{21}N_2O_2$ 321.1598, found 321.1594.

2-Benzyl-N,*N*,4-trimethyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]-indole-1-carboxamide (37). Purification by flash chromatography (from CH_2Cl_2 to 1% CH_2Cl_2–MeOH) gave a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.93 (s, 3H), 2.99 (s, 3H), 3.64 (s, 3H), 3.94 (dd, J = 12.4 and 2.4 Hz, 1H), 4.01 (d, J = 13.2 Hz, 1H), 4.24 (d, J = 13.2 Hz, 1H), 4.32 (dd, J = 12.4 and 4 Hz, 1H), 5.12 (dd, J = 4 and 2.4 Hz, 1H), 7.07 (m, 1H), 7.15 (m, 1H), 7.24–7.43 (m, 7H). ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 31.2 (CH_3), 36.5 (CH_3), 36.8 (CH_3), 51.4 (CH_2), 58.2 (CH_2), 66.8 (CH), 109.7 (CH), 113.9 (C), 118.2 (CH), 119.6 (CH), 120.6 (CH), 122.4 (C), 127.2 (CH), 128.4 (2 CH), 128.8 (2 CH), 139.1 (C), 140.9 (C), 143.2 (C), 171.8 (C). IR (NaCl) ν 2930, 1692, 1637, 1494, 1459, 1381, 1263, 1141, 746 cm^{-1}. ESI-HRMS [M+H]$^+$ calcd for $C_{21}H_{24}N_3O$ 334.1914, found 334.1927.

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