Preparation and palladium-catalysed arylation of indolylzinc halides[1]

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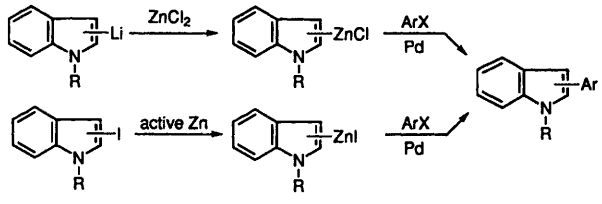
Indolylzinc halides are prepared by two methods: transmetallation of indolyllithiums with zinc chloride and oxidative addition of active zinc to iodoindoles. The palladium-catalysed reaction of the indolylzinc halides provides a practical method for synthesizing arylindoles.

Organozinc derivatives have importance in synthetic organic chemistry because of their reduced reactivity compared with organolithium or organomagnesium halides and their compatibility with functional groups such as alkoxycarbonyl group. Their use has included chemoselective carbon–carbon bond-forming reactions including palladium-catalysed cross-coupling.[2] Organozinc halides have been prepared, in general, by transmetallation of organo-lithium or -magnesium halides with zinc chloride, although this method is essentially limited to the preparation of organozinc halides without functional groups (*e.g.* carbonyl). Direct preparation of organozinc halides by oxidative addition of active zinc to organic iodides or bromides has, however, been reported[3] and this method is suitable for derivatives with functional groups (*e.g.* cyano, acyl or alkoxycarbonyl); it is applicable to both aliphatic and aromatic halides. Application of this method to the preparation of pyridinylzinc halides has already been reported by our group.[4] To our knowledge the synthetic use of indolylzinc halides had not been reported until our communications appeared.[1,5] Here, we report the development of two practical methods for preparing indolylzinc halides and their application to the synthesis of arylindoles by palladium-catalysed reaction with aryl halides (see Scheme 1). One of the preparations of



Scheme 1

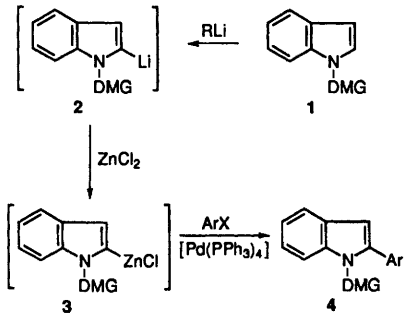
indolylzinc halides is by transmetallation of indolyllithiums with zinc chloride and the other is oxidative addition of active zinc to iodoindoles.

Indolylzinc chlorides from lithioindoles by transmetallation with zinc chlorides

First of all, we examined the preparation of indol-2-ylzinc chlorides from indol-2-yllithiums and their palladium-catalysed reaction with aryl halides. Lithiation of indoles at the 2-position with directed metallation groups (DMGs) at the 1-position has been widely studied, many DMGs having been utilized for this purpose: *e.g.* phenylsulfonyl,[6] methoxymethyl,[6–8] *tert*-butoxycarbonyl,[9–11] lithiooxycarbonyl,[12–15] 2-trimethylsilylethoxymethyl,[16] dimethylaminomethyl,[17,18] methoxy,[20] *N*-*tert*-butylcarbamoyl[21] and methoxymethyl.[22] Our choice of DMGs for our work was dictated by our desire for smooth transmetallation of the lithioindoles with zinc chloride to indolylzinc chlorides combined with easy removal of the DMGs. 2-Lithio-1-methoxymethylindole **2a**[6] prepared from the reaction of 1-(methoxymethyl)indole **1a** with *tert*-butyllithium in THF below −70 °C was treated with zinc chloride at room temperature. The resulting 1-methoxymethyl(indol-2-yl)zinc chloride **3a** reacted with iodobenzene in the presence of tetrakis(triphenylphosphine)palladium in THF under reflux to give 1-methoxymethyl-2-phenylindole **4a** (28%). Similarly, 1-(*N*,*N*-dimethylaminomethyl)-2-lithioindole **2b**[17] was transformed into the indol-2-ylzinc chloride **3b**. The palladium-catalysed phenylation of **3b** afforded not the expected product, 1-(*N*,*N*-dimethylaminomethyl)-2-phenylindole **4b**, but 3-(*N*,*N*-dimethylaminomethyl)-2-phenylindole (15%). Rearrangement of the *N*,*N*-dimethylaminomethyl group from the 1-position to the 3-position of indole has been reported by Hlasta *et al.*[18] and Katritzky *et al.*[19]

1-*tert*-Butoxycarbonylindol-2-ylzinc chloride **3c** prepared from the corresponding 2-lithioindole **2c**[10] was coupled with iodobenzene to yield the 2-phenylindole **4c** (68%).

Lithiation of 1-phenylsulfonylindole **1d** with *tert*-butyllithium[6] followed by transmetallation with zinc chloride and then palladium-catalysed phenylation gave an inseparable mixture of 2-phenyl-1-phenylsulfonylindole **4d** and 1-(2-phenylphenylsulfonyl)indole. Lithiation of **1d** by lithium diisopropylamide (LDA) instead of *tert*-butyllithium at −78 °C followed by the transmetallation and the cross-coupling gave no product. Lithiation by LDA at −20 to 0 °C, however, gave a smooth reaction and afforded **4d** (51%).



1-4	DMG	RLi	Yield (%)
a	CH_2OMe	Bu^tLi	28
b	CH_2NMe_2	BuLi	—*
c	$COOBu^t$	Bu^tLi	68
d	SO_2Ph	LDA	51

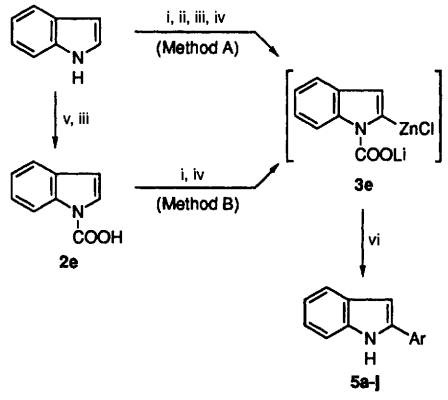
*3-(*N*,*N*-Dimethylaminomethyl)-2-phenylindole was obtained in 15% yield.

Scheme 2

The results described above show that the *tert*-butoxycarbonyl group is the best group for lithiation, transmetallation and

Table 1 Synthesis of 2-arylindoles from 1-lithiooxycarbonylindol-2-ylzinc chloride

Compd.	ArX	Method	Reaction temp.	Reaction time/h	Yield (%)
5a	Iodobenzene	A	Room temp.	18	22
5a	Iodobenzene	B	Reflux	14	74
5b	2-Bromopyridine	A	Room temp.	18	27
5b	2-Iodopyridine	B	Reflux	14	29
5c	2-Iodothiophene	B	Reflux	18	56
5d	4-Nitroiodobenzene	B	Reflux	15	55
5e	Ethyl 4-iodobenzoate	B	Reflux	18	54
5f	4-Methoxyiodobenzene	B	Reflux	18	25
5g	Ethyl 3-iodobenzoate	B	Reflux	18	68
5h	3-Iodo-*N*,*N*-dimethylbenzamide	B	Reflux	15	58
5i	2-Bromo-*N*,*N*-dimethylpyridine-6-carboxamide	B	Reflux	15	29
5j	2-Iodo-*N*,*N*-dimethyl-6-methyl-pyrimidine-4-carboxamide	B	Reflux	11	52



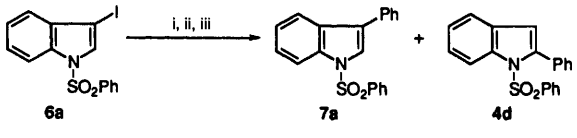
Scheme 3 *Reagents:* i, BuLi, THF; ii, CO_2; iii, Bu^{t}Li; iv, $ZnCl_2$; v, Bu^{t}Li; vi, ArX, $[Pd(PPh_3)_4]$

palladium-catalysed reaction. The lithiooxycarbonyl group was selected as the most easily removable DMG for lithiation of indole at the 2-position. Thus, 1-lithiooxycarbonylindole, prepared from the reaction of indole with butyllithium by Katritzky's method,[12] was lithiated with *tert*-butyllithium and then transmetallated with zinc chloride (Method A) to give lithiooxycarbonylindolylzinc chloride **3e**. This was coupled with iodobenzene and 2-bromopyridine in THF at room temperature to give 2-phenylindole **5a** (22%) and 2-(2-pyridyl)indole **5b** (27%).

In order to improve the yields of **5**, indole-1-carboxylic acid **2e**[23] was lithiated with *tert*-butyllithium (2 equiv.) and subsequently transmetallated with zinc chloride (Method B) to give **3e**. This then underwent a palladium-catalysed reaction with iodobenzene under reflux to afford **5a** (74%).

The coupling reaction of **3e** with various aryl halides containing ethoxycarbonyl, *N*,*N*-dimethylcarbamoyl or nitro groups gave the corresponding 2-arylindoles **5b–j** in the yields shown in Table 1.

Hydrogen–lithium exchange at the 3-position of indoles having DMGs at the 2-position has been reported.[24–26] 3-Lithiation of indole derivatives unsubstituted at the 2-position, however was generally performed by halogen–lithium exchange.[27,28] 3-Iodo-1-phenylsulfonylindole was lithiated with *tert*-butyllithium at −100 °C, and the resulting lithioindoles were subsequently transmetallated with zinc chloride at a temperature not exceeding −85 °C. Cross-coupling of the indolylzinc chloride with iodobenzene gave a mixture of 3-phenyl **7a** and 2-phenyl derivatives **4d** in quantitative yield. The



Scheme 4 *Reagents:* i, Bu^{t}Li, THF; ii, $ZnCl_2$; iii, PhI, $[Pd(PPh_3)_4]$

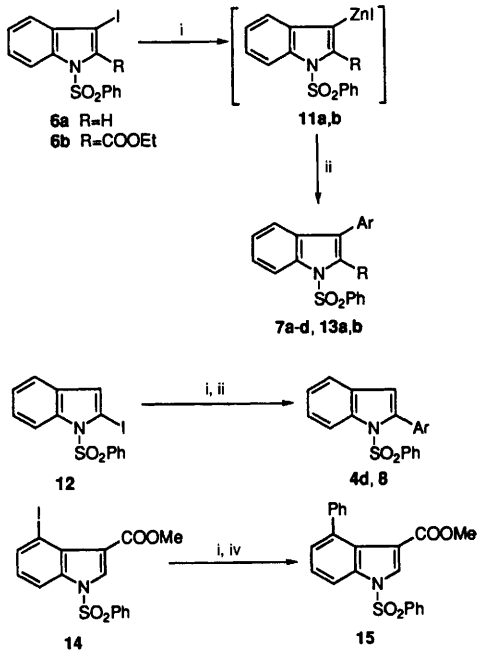
^{1}H NMR analysis elucidated the ratio of the mixture to be *ca.* 1:1. Although it was found that selective preparation of indol-3-ylzinc chlorides from 3-lithioindoles unsubstituted at the 2-position is difficult, oxidative addition of active zinc to 3-iodoindoles solved the problem (see later).

Recently, halogen–lithium exchange with *tert*-butyllithium of 3-(*N*,*N*-dimethylaminomethyl)-1-(triisopropylsilyl)indole **9** at the 4-position was reported.[29] Transmetallation of the lithiated **9** with zinc chloride and subsequent palladium-catalysed reaction with iodobenzene and 3-iodopyridine gave the corresponding 4-phenyl- **10a** (58%) and 4-(3-pyridyl)indole **10b** (50%).

Scheme 5 *Reagents:* i, Bu^{t}Li, THF; ii, $ZnCl_2$; iii, ArX, $[Pd(PPh_3)_4]$

Indolylzinc iodides from iodoindoles by oxidative addition with active zinc

We have already reported the preparation and reaction of pyridylzinc halides by oxidative addition of active zinc with halogenopyridines,[4] a method now applied to iodoindoles to prepare indolylzinc iodides. Initially, preparation of 1-



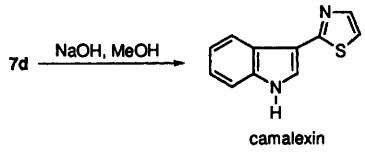
Scheme 6 *Reagents:* i, active Zn, THF; ii, ArX, $[Pd(PPh_3)_4]$; iii, active Zn, THF; iv, PhI, $Pd(PPh_3)_4$

Table 2 Synthesis of arylindoles from 1-phenylsulfonylindolylzinc iodides

Halogenoindole	ArX	Reaction temp.	Product	Yield (%)
6a	Iodobenzene	Room temp.	**7a**	83
6a	2-Bromopyridine	Room temp.	**7b**	72
6a	3-Iodopyridine	Room temp.	**7c**	72
6a	2-Iodothiazole	Room temp.	**7d**	73
6b	Iodobenzene	Reflux	**13a**	44
6b	2-Bromopyridine	Reflux	**13b**	44
11	Iodobenzene	Room temp.	**4d**	57
11	2-Bromopyridine	Room temp.	**8b**	45
14	Iodobenzene	Room temp.	**15**	43

phenylsulfonylindol-3-ylzinc iodide **11a** was examined, since selective preparation of 1-phenylsulfonylindol-3-ylzinc chloride was difficult as described above.

3-Iodo-1-phenylsulfonylindole **6a** reacted with active zinc in THF at room temperature to give the indolylzinc iodide **11a**. This was coupled with iodobenzene to give the 3-phenylindole **7a** (83%) without any 2-phenylindole **4d**. Similar reaction with 2-bromopyridine, 3-iodopyridine or 2-iodothiazole afforded the corresponding products **7b–d** in the yields shown in Table 2. Alkaline hydrolysis of compound **7d** gave camalexin, 3-thiazol-2-ylindole (83%), which is a simple phytoalexin produced in the leaves of *Camelina sative* (Cruciferae) in response to infection by the fungus *Alternara brassicae*.[30,31]



Scheme 7

The method was also applicable to the iodoindoles having an alkoxycarbonyl group. Thus, a similar reaction of ethyl 3-iodo-1-phenylsulfonylindole-2-carboxylate **11b** yielded the ethyl 3-arylindole-2-carboxylates **13a** (44%) and **13b** (54%).

2-Iodo-1-phenylsulfonylindole **12** and methyl 4-iodo-1-phenylsulfonyl indole-3-carboxylate **14** were analogously treated with active zinc and the products subsequently coupled indolylzinc iodides to afford the arylindole derivatives **8a,b** and **15**.

Conclusions

Preparation of indolylzinc halides by the transmetallation from lithioindoles was easily achieved except for compounds having no 2-substituents. However, indolylzinc iodides can be generally prepared by oxidative addition of active zinc with iodoindoles. Indolylzinc halides are useful synthetic intermediates for the introduction of carbon substituents into indole derivatives, especially for those having carbonyl groups; moreover, their stability at room temperature is advantageous in synthetic chemistry.

Experimental

General details

THF and Et_2O were distilled from sodium–benzophenone ketyl before use. BuLi and Bu^{t}Li were titrated using 2,5-dimethoxybenzyl alcohol[32] before use. $[Pd(PPh_3)_4]$ was prepared from $[Pd(PPh_3)_2Cl_2]$, PPh_3 and BuLi (1:2:2).[4b] 1 M $ZnCl_2$ in THF solution was prepared by dissolving $ZnCl_2$ (100 mmol) melted under reduced pressure in dry THF (100 ml). All melting points and boiling points are uncorrected. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^1H NMR spectra were recorded on a JEOL JNM-PMX60 (60 MHz) and a Hitachi R-3000 (300 MHz) spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) or 2,2-dimethylsilapentanesulfonic acid sodium salt (DSS) used as the internal references; coupling constants are expressed in Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet and br = broad. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a JMS-DX303 and a JMS-AX500 instruments.

1-Phenylsulfonylindole 1d

To a vigorously stirred mixture of indole (5.85 g, 50 mmol), 50% aq. NaOH (50 ml), water (75 ml) and tetrabutylammonium bromide (1.61 g, 5 mmol), was dropwise added $PhSO_2Cl$ (9.71 g, 55 mmol) in benzene (50 ml). After the mixture had been stirred at room temperature for 1 h, it was washed with 1 M aq. $NaHCO_3$ (30 ml), water (30 ml) and saturated brine (30 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallized from Et_2O–hexane to give colourless needles (11.67 g, 90%), mp 76.5–77 °C (lit.,[27] mp 76–76.5 °C); δ_H(300 MHz; $CDCl_3$–TMS) 6.66 (1 H, dd, *J* 0.7, 2.7), 7.10–7.60 (7 H, m), 7.80–7.90 (2 H, m) and 8.00 (1 H, d, *J* 8.8); $\nu_{max}(CHCl_3)/cm^{-1}$ 1370 and 1170.

1-Methoxymethyl-2-phenylindole 4a

To a solution of 1-methoxymethylindole **1a**[6] (0.81 g, 5 mmol) in THF (15 ml), 1.22 M Bu^{t}Li in pentane (4.7 ml, 5.75 mmol) was added at < −70 °C under an argon atmosphere. Stirring was continued for 1 h after which 1 M $ZnCl_2$ in THF (6.5 ml, 6.5 mmol) was added at the same temperature. After continued stirring for 30 min, the mixture was warmed to room temperature and treated with a solution of iodobenzene (1.5 g, 7.5 mmol) in THF (3 ml) and $[Pd(PPh_3)_4]$ (0.25 mmol) in THF (3 ml). The mixture was then refluxed for 14 h after which it was diluted with water and $CHCl_3$ and then filtered through a Celite® pad. The filtrate was extracted with $CHCl_3$ (50 ml × 3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel (50 g) column chromatography using AcOEt–hexane (1:9) as eluent. Further purification of the product by preparative silica gel thin-layer chromatography using AcOEt–hexane (1:19) gave a pale yellow viscous liquid (0.33 g, 28%); δ_H(60 MHz; $CDCl_3$–TMS) 3.23 (3 H, s), 5.37 (2 H, s), 6.57 (1 H, s) and 7.0–7.8 (9 H, m); *m/z* 237 (M^+) [Found (HRMS): *m/z* 237.1127. Calc. for $C_{16}H_{15}NO$: 237.1153].

3-(*N*,*N*-Dimethylaminomethyl)-2-phenylindole

To a solution of 1-(*N*,*N*-dimethylaminomethyl)indole **1b**[17] (0.87 g, 5 mmol) in THF (30 ml), 1.2 M BuLi in hexane (4.6 ml, 5.5 mmol) was added < −70 °C under an argon atmosphere. The mixture was stirred for 30 min at the same temperature, after which it was warmed to 0 °C during 30 min and then cooled to −70 °C. 1 M $ZnCl_2$ in THF (6 ml, 6 mmol) was added at < −70 °C to the mixture which was then stirred at this temperature for 30 min before it was warmed to room temperature. A solution of iodobenzene (2.0 g, 10 mmol) in THF (2 ml) and $[Pd(PPh_3)_4]$ (0.25 mmol) in THF (2 ml) was added to the mixture which was then refluxed for 16 h. After this it was diluted with water and $CHCl_3$, filtered through a

Celite® pad and extracted with $CHCl_3$ (50 ml × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel (50 g) column chromatography using $CHCl_3$ and Et_3N–$CHCl_3$ (1:19) as eluents. The crude product obtained from the Et_3N–$CHCl_3$ (1:19) eluate was recrystallized from AcOEt–hexane to give colourless prisms (0.19 g, 15%), mp 128–129 °C (lit.,[33] mp 130–130.8 °C); δ_H(60 MHz; $CDCl_3$–TMS) 2.27 (6 H, s), 3.63 (2 H, s), 7.0–7.9 (9 H, m) and 8.2 (1 H, br s); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450.

1-*tert*-Butoxycarbonyl-2-phenylindole 4c

To a solution of 1-*tert*-butoxycarbonylindole **1c**[10] (1.1 g, 5 mmol) in THF (20 ml), 1.22 M Bu^{t}Li in pentane (4.5 ml, 5.5 mmol) was added < −70 °C under an argon atmosphere, and stirring was continued for 1 h. 1 M $ZnCl_2$ in THF (6 ml, 6 mmol) was added at the same temperature after which the mixture was warmed to room temperature during 3 h. A solution of iodobenzene (1.3 g, 6.5 mmol) in THF (2 ml) and [$Pd(PPh_3)_4$] (0.05 mmol) in THF (2 ml) was added to the mixture which was then refluxed for 18 h. The reaction mixture was diluted with water and $CHCl_3$, filtered through a Celite® pad and then extracted with $CHCl_3$ (70 ml × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel (70 g) column chromatography using Et_2O–hexane (1:150, 1:50 and 1:19) as eluents. The crude product obtained from the Et_2O–hexane (1:50) eluate was recrystallized from Et_2O–hexane to give colourless prisms (1.0 g, 68%), mp 76–77 °C; δ_H(60 MHz; $CDCl_3$–TMS) 1.30 (9 H, s), 6.53 (1 H, s) and 7.1–8.3 (9 H, m); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730; *m/z* 293 (M^+) [Found (HRMS): *m/z* 293.1450. Calc. for $C_{19}H_{19}NO_2$: 293.1415] (Found: C, 77.66; H, 6.64; N, 4.88. Calc. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77%).

Preparation of 2-arylindoles from indole: general procedure A

To a solution of indole in THF, BuLi in hexane was added at < −50 °C, and the mixture was stirred for 30 min at −78 °C under an argon atmosphere. After introduction of dry CO_2 gas for 3–5 min, the THF was evaporated under reduced pressure at room temperature. The residue was dissolved in THF (15 ml) and the solution cooled at −78 °C. Bu^{t}Li in pentane was added at < −50 °C, and the mixture was stirred at the same temperature for 1 h. 1 M $ZnCl_2$ in THF was added to the mixture which was then warmed to room temperature during 1–2 h. A solution of aryl halides in THF and [$Pd(PPh_3)_4$] in THF was added to the mixture which was allowed to react at the required temperature (for the appropriate time see Table 1). The reaction mixture was diluted with water and $CHCl_3$, and filtered through a Celite® pad. The aqueous layer was neutralized with NH_4Cl and extracted with $CHCl_3$ (50 ml × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure.

Preparation of 2-arylindoles from indole-1-carboxylic acid: general procedure B

To a THF solution of indole-1-carboxylic acid **2e**[23] dried under reduced pressure, Bu^{t}Li in pentane was added at < −65 °C under argon atmosphere. The mixture was stirred at −70 °C for 1.5 h after which 1 M $ZnCl_2$ in THF was added. The mixture was warmed to room temperature during 1–2 h after which a solution of aryl halides in THF and [$Pd(PPh_3)_4$] in THF was added to it. The mixture was allowed to react at the required temperature (for the appropriate time see Table 1). The reaction mixture was treated as described in general procedure A.

2-Phenylindole 5a

(a) According to general procedure A. The crude product obtained using indole (0.59 g, 5 mmol), 1.32 M BuLi in hexane (4.0 ml, 5.25 mmol), 1.26 M Bu^{t}Li in pentane (4.2 ml, 5.25 mmol), 1 M $ZnCl_2$ in THF (6.0 ml, 6.0 mmol), iodobenzene (1.22 g, 6 mmol) and [$Pd(PPh_3)_4$] (0.25 mmol), was purified by silica gel (50 g) column chromatography using AcOEt–hexane (1:9) as eluent. The crude product was distilled at 100 °C/6 mmHg to remove the starting indole, and the residue was recrystallized from Et_2O–hexane to give colourless scales (0.21 g, 22%).

(b) According to general procedure B. The crude product obtained from the reaction using indole-1-carboxylic acid **2e** (0.81 g, 5 mmol), 1.20 M Bu^{t}Li in pentane (8.8 ml, 6.0 mmol), 1 M $ZnCl_2$ in THF (6.5 ml, 6.5 mmol), iodobenzene (0.62 g, 3 mmol) and [$Pd(PPh_3)_4$] (0.25 mmol), was purified by silica gel (50 g) column chromatography using AcOEt–hexane (1:9) as eluent. The crude product was distilled at 100 °C/6 mmHg to remove the starting indole, and the residue was recrystallized from Et_2O–hexane to give colourless scales (0.43 g, 74%), mp 189 °C (lit.,[34] mp 187–188 °C); δ_H(60 MHz; $CDCl_3$–TMS) 6.60 (1 H, d, *J* 2), 7.0–7.8 (9 H, m) and 8.2 (1 H, br s); $\nu_{max}(CHCl_3)/cm^{-1}$ 3470; *m/z* 193 (M^+) [Found (HRMS): *m/z* 193.0897. Calc. for $C_{14}H_{11}N$: 193.0891].

2-(2-Pyridyl)indole 5b

(a) According to general procedure A. The crude product obtained using indole (0.82 g, 7.0 mmol), 1.50 M BuLi in hexane (4.9 ml, 7.35 mmol), 1.27 M Bu^{t}Li in pentane (5.8 ml, 7.35 mmol), 1 M $ZnCl_2$ in THF (8.4 ml, 8.4 mmol), 2-bromopyridine (1.11 g, 7.0 mmol), and [$Pd(PPh_3)_4$] (0.35 mmol), was purified by silica gel (100 g) column chromatography using AcOEt–hexane (1:9) as eluent. The product was recrystallized from Et_2O–hexane to give colourless needles (0.36 g, 27%).

(b) According to general procedure B. The crude product obtained using indole-1-carboxylic acid **2e** (0.48 g, 3 mmol), 1.20 M Bu^{t}Li in pentane (5.3 ml, 6.3 mmol), 1 M $ZnCl_2$ in THF (4.0 ml, 4.0 mmol), 2-iodopyridine (0.80 g, 4 mmol) and [$Pd(PPh_3)_4$] (0.15 mmol), was purified by silica gel (50 g) column chromatography using AcOEt–hexane (1:9) as eluent. The product was recrystallized from Et_2O–hexane to give colourless needles (0.17 g, 29%), mp 156–157 °C (lit.,[35] mp 152 °C); δ_H(300 MHz; $CDCl_3$–TMS) 7.02 (1 H, s), 7.10–7.30 (3 H, m), 7.41 (1 H, d, *J* 8.0), 7.60–7.80 (3 H, m), 8.57 (1 H, d, *J* 4.4) and 9.64 (1 H, br s); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450; *m/z* 194 (M^+).

2-(2-Thienyl)indole 5c

According to general procedure B. The crude product obtained using indole-1-carboxylic acid **2e** (0.81 g, 5 mmol), 1.24 M Bu^{t}Li in pentane (8.5 ml, 10.5 mmol), 1 M $ZnCl_2$ in THF (6.5 ml, 6.5 mmol), 2-iodothiophene (1.40 g, 6.5 mmol) and [$Pd(PPh_3)_4$] (0.25 mmol), was purified by silica gel (40 g) column chromatography using Et_2O–hexane (1:4) as eluent. The product was recrystallized from Et_2O–hexane to give colourless needles (0.56 g, 56%), mp 172–173 °C (lit.,[36] mp 169 °C); δ_H(60 MHz; $CDCl_3$–TMS) 6.60 (1 H, d, *J* 2), 6.8–7.6 (6 H, m) and 8.1 (1 H, br s).

2-(4-Nitrophenyl)indole 5d

According to general procedure B. The crude product obtained using indole-1-carboxylic acid **2e** (0.48 g, 3 mmol), 1.23 M Bu^{t}Li in pentane (5.2 ml, 6.3 mmol), 1 M $ZnCl_2$ in THF (3.9 ml, 3.9 mmol), 4-nitroiodobenzene (0.97 g, 3.9 mmol) and [$Pd(PPh_3)_4$] (0.15 mmol), was purified by silica gel (40 g) column chromatography using Et_2O–hexane (1:4) as eluent. The product was recrystallized from acetone–hexane to give a yellow powder (0.39 g, 55%), mp 250–251 °C (lit.,[37] mp 251–252 °C); δ_H(60 MHz; [$^2H_6$]DMSO–DSS) 7.0–7.8 (5 H, m), 8.16 (2 H, d, *J* 8), 8.42 (1 H, d, *J* 8) and 11.9 (1 H, br s).

Ethyl 4-indo-2-ylbenzoate 5e

According to general procedure B. The crude product obtained using indole-1-carboxylic acid **2e** (0.48 g, 3 mmol), 1.23 M Bu^{t}Li in pentane (5.2 ml, 6.3 mmol), 1 M $ZnCl_2$ in THF (3.9 ml, 3.9 mmol), ethyl 4-iodobenzoate (1.1 g, 3.9 mmol), and [$Pd(PPh_3)_4$] (0.15 mmol), was purified by silica gel (50 g) column chromatography using Et_2O–hexane (1:9, 3:17, 1:4, and 1:3) as eluents. The product obtained from the Et_2O–

hexane (1:4) eluate was recrystallized from acetone to give an orange yellow powder. (0.43 g, 54%), mp 214–215 °C; δ_H(300 MHz; $CDCl_3$, [$^2H_6$]DMSO–TMS) 1.42 (3 H, t, *J* 7.0), 4.39 (2 H, q, *J* 7.0), 6.92 (1 H, s), 7.00–7.20 (2 H, m), 7.40–7.60 (2 H, m), 7.88 (2 H, d, *J* 8.4), 8.07 (2 H, d, *J* 8.4) and 10.97 (1 H, br s); ν_{max}(KBr)/cm^{-1} 1690 and 1610; *m/z* 265 (M^+) [Found (HRMS): *m/z* 265.1072. Calc. for $C_{17}H_{15}NO_2$: 265.1103].

2-(4-Methoxyphenyl)indole 5f

According to general procedure B. The crude product obtained using indole-1-carboxylic acid **2e** (0.48 g, 3 mmol), 1.23 M Bu^{t}Li in pentane (5.4 ml, 6.6 mmol), 1 M $ZnCl_2$ in THF (3.9 ml, 3.9 mmol), 4-methoxyiodobenzene (0.91 g, 3.9 mmol) and [$Pd(PPh_3)_4$] (0.15 mmol), was purified by silica gel (50 g) column chromatography using AcOEt–hexane (1:4) as eluent. The product was recrystallized from acetone to give colourless scales (0.17 g, 25%), mp 233–234 °C (lit.,[37] mp 230–230.5 °C); δ_H(60 MHz; $CDCl_3$–[$^2H_6$]DMSO–DSS) 3.83 (3 H, s), 6.72 (1 H, d, *J* 2), 6.9–7.9 (8 H, m) and 11.4 (1 H, br s).

Ethyl 3-iodobenzoate

A mixture of 3-iodobenzoic acid (7.44 g, 30 mmol) and $SOCl_2$ (20 ml) was refluxed for 2 h after which the excess of $SOCl_2$ was removed by evaporation under reduced pressure at the residue treated with EtOH (20 ml). This mixture was refluxed for 1 h, after which the EtOH was removed by evaporation and the residue was mixed with water and extracted with $CHCl_3$. The extract was washed with 0.5 M aq. $NaHCO_3$ dried ($MgSO_4$) and evaporated. The residue was distilled *in vacuo* to give a colourless liquid (7.96 g, 96%), bp 119–120 °C/5 mmHg. (lit.,[38] bp 97–98 °C/2 mmHg); δ_H(60 MHz; $CDCl_3$–TMS)] 3.05 (3 H, t, *J* 6), 4.33 (2 H, q, *J* 7), 6.9–7.3 (1 H, m), 7.7–8.1 (2 H, m) and 8.2–8.4 (1 H, m); ν_{max}($CHCl_3$)/cm^{-1} 1720; *m/z* 276 (M^+) [Found (HRMS): *m/z* 275.9662. Calc. for $C_9H_9IO_2$: 275.9646].

Ethyl 3-indol-2-ylbenzoate 5g

According to general procedure B. The crude product obtained using indole-1-carboxylic acid **2e** (1.7 g, 10 mmol), 1.24 M Bu^{t}Li in pentane (17 ml, 21 mmol), 1 M $ZnCl_2$ in THF (13 ml, 13 mmol), ethyl 3-iodobenzoate (3.6 g, 13 mmol), and [$Pd(PPh_3)_4$] (0.5 mmol), was purified by silica gel (50 g) column chromatography using AcOEt–hexane (1:9) as eluent. The product was recrystallized from Et_2O–hexane to give colourless needles (1.8 g, 68%), mp 129–130 °C; δ_H(60 MHz; $CDCl_3$–TMS) 1.40 (3 H, t, *J* 7), 4.43 (2 H, q, *J* 3.5), 6.85 (1 H, d, *J* 2), 7.0–8.2 (7 H, m), 8.3–8.4 (1 H, m) and 8.5 (1 H, br s); ν_{max}($CHCl_3$)/cm^{-1} 3470 and 1720 (Found: C, 77.17; H, 5.76; N, 5.31. Calc. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28%).

3-Iodo-*N*,*N*-dimethylbenzamide

A mixture of 3-iodobenzoic acid (7.44 g, 30 mmol) and $SOCl_2$ (20 ml) was refluxed for 1 h after which the excess of $SOCl_2$ was removed by evaporation under reduced pressure. The residue was poured into ice-cold 40% aq. Me_2NH (10 ml) and the mixture stirred at room temperature for 30 min; it was then diluted with water and extracted with $CHCl_3$. The extract was dried (K_2CO_3) and evaporated under reduced pressure and the residue was distilled *in vacuo* to give a pale yellow viscous liquid (7.49 g, 91%), bp 140–145 °C/1 mmHg; δ_H(60 MHz; $CDCl_3$–TMS): 3.02 (6 H, br s), 6.9–7.5 (2 H, m) and 7.6–7.9 (2 H, m); ν_{max}($CHCl_3$)/cm^{-1} 1630; *m/z* 275 (M^+) [Found (HRMS): *m/z* 274.9802. Calc. for $C_9H_{10}INO$: 274.9805].

2-Indol-2-yl-*N*,*N*-dimethylbenzamide 5h

According to general procedure B. The crude product obtained using indole-1-carboxylic acid **2e** (1.7 g, 10 mmol), 1.22 M Bu^{t}Li in pentane (17 ml, 21 mmol), 1 M $ZnCl_2$ in THF (13 ml, 13 mmol), 3-iodo-*N*,*N*-dimethylbenzamide (3.6 g, 13 mmol), and [$Pd(PPh_3)_4$] (0.5 mmol), was purified by silica gel (50 g) column chromatography using AcOEt–hexane (1:2) as eluent. The crude product was distilled at 135 °C/1 mmHg to remove the starting pyridine, and the residue was recrystallized from acetone to give colourless needles (1.54 g, 58%), mp 178–179 °C; δ_H(60 MHz; $CDCl_3$–TMS) 3.1 (6 H, br s), 6.74 (1 H, d, *J* 2), 7.0–7.8 (8 H, m) and 9.3 (1 H, br s); ν_{max}($CHCl_3$)/cm^{-1} 3470 and 1630 (Found: C, 77.08; H, 6.05; N, 10.62. Calc. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60%).

6-Bromo-*N*,*N*-dimethylpyridine-2-carboxamide

A mixture of 2-bromo-6-methylpyridine (30.58 g, 178 mmol) and $KMnO_4$ (62 g, 390 mmol) in water (500 ml) was refluxed for 18 h after which further $KMnO_4$ (10 g, 63 mmol) was added, and refluxing continued for 6 h. The hot reaction mixture was filtered to remove MnO_2, and the MnO_2 was washed with hot water and Et_2O. The aqueous filtrate was extracted with Et_2O and the extract dried (K_2CO_3) and worked up to give recovery of starting material (7.8 g, 26%). The aqueous layer was concentrated under reduced pressure and acidified with conc. HCl to precipitate a solid which was filtered off. A mixture of solid and $SOCl_2$ (200 ml) was refluxed for 12 h after which the excess of $SOCl_2$ was removed by evaporation under reduced pressure. The residue was dissolved in dry benzene (100 ml), to which was added dropwise 40% aq. Me_2NH (50 ml). The mixture was stirred at room temperature for 1 h after which the benzene layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was distilled *in vacuo* to give a colourless liquid (14.7 g, 36%), bp 130–135 °C/1 mmHg; δ_H(60 MHz; $CDCl_3$–TMS) 3.03 (3 H, s), 3.13 (3 H, s) and 7.1–7.8 (3 H, m); ν_{max}($CHCl_3$)/cm^{-1} 1640; *m/z* 228 (M^+) [Found (HRMS): *m/z* 227.9893. Calc. for $C_8H_9{}^{79}BrN_2O$: 227.9898].

6-Indol-2-yl-*N*,*N*-dimethylpyridine-2-carboxamide 5i

According to general procedure B. The crude product obtained using indole-1-carboxylic acid **2e** (1.7 g, 10 mmol), 1.22 M Bu^{t}Li in pentane (17 ml, 21 mmol), 1 M $ZnCl_2$ in THF (13 ml, 13 mmol), 6-bromo-*N*,*N*-dimethylpyridine-2-carboxamide (2.9 g, 13 mmol) and [$Pd(PPh_3)_4$] (0.5 mmol), was purified by silica gel (50 g) column chromatography using AcOEt–hexane (4:1) as eluent. The product was distilled at 135 °C/1 mmHg to remove the starting pyridine, and the residue was recrystallized from acetone–hexane to give colourless needles (0.72 g, 29%), mp 176–177 °C δ_H(60 MHz; $CDCl_3$–TMS) 3.18 (6 H, d, *J* 5), 7.0–7.9 (8 H, m) and 9.5 (1 H, br s); ν_{max}($CHCl_3$)/cm^{-1} 3460, 1640, 1595 and 1570 (Found: C, 72.44; H, 5.64; N, 15.78. Calc. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.78; N, 15.84%).

1,2-Dihydro-*N*,*N*,6-trimethyl-2-oxopyrimidine-4-carboxamide

A mixture of methyl 1,2-dihydro-6-methyl-2-oxopyrimidine-4-carboxylate urea adduct[39] (2.28 g, 10 mmol) and 50% aq. Me_2NH (5 ml) was stirred at room temperature overnight. The solid gradually dissolved, and the orange colour of the reaction mixture turned to yellow. The solvent was removed under reduced pressure, and the residue was dissolved in a small amount of water. The aqueous solution was adjusted to PH 4 after which it was continuously extracted with $CHCl_3$. The extract was evaporated under reduced pressure and the residue was recrystallized from MeOH–AcOEt to give colourless needles (0.83 g, 46%), mp 201–203 °C (decomp.); δ_H(60 MHz; $CDCl_3$–TMS) 2.45 (3 H, s), 3.10 (6 H, d, *J* 2), 6.50 (1 H, s) and 12.5–14.5 (1 H, br); ν_{max}($CHCl_3$)/cm^{-1} 1660 and 1620 (Found: C, 53.02; H, 6.13; N, 23.30. Calc. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19%).

2-Chloro-*N*,*N*,6-trimethylpyrimidine-4-carboxamide

A mixture of 1,2-dihydro-*N*,*N*,6-trimethyl-2-oxopyrimidine-4-carboxamide (1.8 g, 10 mmol) and $POCl_3$ (20 ml) was refluxed for 10 min after which it was mixed with ice–water, made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was dried (K_2CO_3) and evaporated under reduced pressure and the residue was purified by alumina column chromatography using $CHCl_3$ as eluent. The crude product was recrystallized

from Et_2O–hexane to give colourless prisms (1.03 g, 52%), mp 110–111 °C; δ_H(60 MHz; $CDCl_3$–TMS) 2.60 (3 H, s), 3.09 (3 H, s), 3.11 (3 H, s) and 7.40 (1 H, s); $\nu_{max}(CHCl_3)/cm^{-1}$ 1650 (Found: C, 48.21; H, 4.91; Cl, 17.50; N, 21.20. Calc. for $C_8H_{10}ClN_3O$: C, 48.13; H, 5.05; Cl, 17.76; N, 21.05%).

2-Iodo-*N*,*N*,6-trimethylpyrimidine-4-carboxamide

A mixture of 2-chloro-*N*,*N*,6-trimethylpyrimidine-4-carboxamide (3.0 g, 15 mmol) and 57% aq. HI (10 ml) was stirred at room temperature for 1 h after which it was diluted with water, made alkaline with K_2CO_3 and treated with Na_2SO_3. The aqueous layer was extracted with $CHCl_3$ and the extract was dried (K_2CO_3) and evaporated. Recrystallization of the residue from acetone–hexane gave colourless prisms (4.0 g, 92%), mp 110–111 °C; δ_H(60 MHz; $CDCl_3$–TMS) 2.53 (3 H, s), 3.11 (6 H, s) and 7.43 (1 H, s); $\nu_{max}(CHCl_3)/cm^{-1}$ 1650 (Found: C, 33.02; H, 3.45; I, 43.78; N, 14.50. Calc. for $C_8H_{10}IN_3O$: C, 33.01; H, 3.46; I, 43.60; N, 14.44%).

2-Indol-2-yl-*N*,*N*,6-trimethylpyrimidine-4-carboxamide 5j

According to general procedure B. The crude product obtained using indole-1-carboxylic acid **2e** (1.7 g, 10 mmol), 1.22 M Bu^{t}Li in pentane (17 ml, 21 mmol), 1 M $ZnCl_2$ in THF (13 ml, 13 mmol), 2-iodo-*N*,*N*,6-trimethylpyrimidine-4-carboxamide (3.8 g, 13 mmol) and [$Pd(PPh_3)_4$] (0.5 mmol) was purified by silica gel (50 g) column chromatography using AcOEt–hexane (1:1) as an eluent. The product was recrystallized from acetone to give colourless needles (1.46 g, 52%), mp 182–183 °C; δ_H(60 MHz; $CDCl_3$–TMS) 2.53 (3 H, s), 3.13 (6 H, d, *J* 2), 6.9–7.8 (6 H, m) and 9.5 (1 H, br s); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 1640, 1560 and 1540 (Found: C, 68.81; H, 5.78; N, 20.07. Calc. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99%).

3-(*N*,*N*-Dimethylaminomethyl)-4-phenyl-1-(triisopropylsilyl)-indole 10a

To a solution of 3-(*N*,*N*-dimethylaminomethyl)-1-(triisopropylsilyl)indole **9** (0.33 g, 1 mmol) in Et_2O (4 ml) was added 0.86 M Bu^{t}Li in pentane (1.4 ml, 1.2 mmol) at < −65 °C under an argon atmosphere. The mixture was stirred for 1 h at < −70 °C and then warmed to 0 °C during 1 h. After the mixture had been cooled again to −70 °C, it was treated with 1 M $ZnCl_2$ in THF (1.2 ml, 1.2 mmol) and then allowed to warm to room temperature. A solution of iodobenzene (0.25 g, 1.2 mmol) in THF (2 ml) and [$Pd(PPh_3)_4$] (0.05 mmol) in THF (2 ml) was added to the mixture which was then refluxed for 24 h. After this it was diluted with water and $CHCl_3$ and filtered through a Celite® pad. The aqueous layer was separated and extracted with $CHCl_3$ (25 ml × 3) and the combined extracts were washed with saturated brine (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel (16 g) column chromatography using AcOEt–hexane (2:3) and Et_3N–hexane (1:4) as eluents. The Et_3N–hexane (1:4) eluate gave a pale yellow viscous liquid (0.24 g, 58%); δ_H(300 MHz; $CDCl_3$–TMS) 1.17 (18 H, d, *J* 7.7), 1.66–1.78 (3 H, m), 1.92 (6 H, s), 3.06 (2 H, s), 6.95 (1 H, d, *J* 7.0) and 7.10–7.50 (8 H, m); *m*/*z* 406 (M^+) [Found (HRMS): *m*/*z* 406.2791. Calc. for $C_{26}H_{38}N_2Si$: 406.2804].

3-(*N*,*N*-Dimethylaminomethyl)-4-(3-pyridyl)-1-(triisopropylsilyl)indole 10b

To a solution of 3-(*N*,*N*-dimethylaminomethyl)-1-(triisopropylsilyl)indole **9** (0.33 g, 1 mmol) in Et_2O (4 ml), was added 0.86 M Bu^{t}Li in pentane (1.4 ml, 1.2 mmol) at < −65 °C under an argon atmosphere. The mixture was stirred for 1 h at < −70 °C and then allowed to warm to 0 °C during 1 h. After cooling again to −70 °C, the mixture was treated with 1 M $ZnCl_2$ in THF (1.2 ml, 1.2 mmol) and warmed to room temperature. A solution of 3-iodopyridine (0.24 g, 1.2 mmol) in THF (2 ml) and [$Pd(PPh_3)_4$] (0.05 mmol) in THF (2 ml) was added to the mixture which was then refluxed for 24 h. After this it was diluted with water and $CHCl_3$ and filtered through a Celite® pad. The aqueous layer was extracted with $CHCl_3$ (25 ml × 3) and the combined extracts were washed with saturated brine (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel (16 g) column chromatography using AcOEt–hexane (2:3) and Et_3N–hexane (1:9). The Et_3N–hexane (1:9) eluate gave a pale yellow viscous liquid (0.21 g, 50%); δ_H(300 MHz; $CDCl_3$–TMS) 1.17 (18 H, d, 7.3), 1.72–1.79 (3 H, m), 1.89 (6 H, s), 3.02 (2 H, s), 6.90–7.90 (6 H, m), 8.58–8.60 (1 H, m) and 8.73–8.74 (1 H, m); *m*/*z* 407 (M^+) [Found (HRMS): *m*/*z* 407.2741. Calc. for $C_{25}H_{37}N_3Si$: 407.2757].

Preparation of active zinc

A mixture of naphthalene (1.85 g, 14.4 mmol) dried under reduced pressure, lithium (42 mg, 6 mmol) washed with THF and THF (4 ml) was stirred whilst undergoing ultrasonication at room temperature for 2–3 h under argon atmosphere to give a dark greenish solution of lithium naphthalenide in THF. Slow addition of 1 M $ZnCl_2$ in THF (3.1 ml, 3.1 mmol) to this gave an exothermic reaction after which the mixture was centrifuged (2500 rpm, 20 min) and the supernatant was discarded. The remained residue was used as active zinc (3 mmol) for oxidative addition to iodoindoles.

Synthesis of arylindoles from indolylzinc iodides prepared by the reaction of iodoindoles and active zinc

General procedure C. A mixture of active zinc (3 mmol) and an iodoindole (1 mmol) in THF (4 ml) was stirred at room temperature for **1–2** h under an argon atmosphere. After disappearance of the starting iodoindole (monitored by thin-layer chromatography) the mixture was centrifuged (2500 rpm, 20 min). The supernatant was added to a suspension of an aryl halide (**1–2** mmol) and [$Pd(PPh_3)_4$] (0.05 mmol) in THF (4 ml), and the mixture was allowed to react at the required temperature (see Table 2) for 18 h. The reaction mixture was diluted with water and $CHCl_3$ and then filtered through a Celite® pad. The aqueous layer was extracted with $CHCl_3$ (30 ml × 3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure.

3-Iodo-1-phenylsulfonylindole 6a

A mixture of indole (5.9 g, 50 mmol) and powdered KOH (10.5 g, 190 mmol) in DMF (25 ml) was stirred for 5 min after which it was treated with I_2 (13.4 g, 53 mmol) in DMF (25 ml), and stirring continued at room temperature for 10 min. The reaction mixture was poured into a mixture of $NaHSO_3$ (5.0 g), 25% aqueous NH_3 (50 ml) and water (750 ml) to afford a precipitate. This was filtered off and rapidly added to a mixture of 50% aq. NaOH (50 ml), water (75 ml) and tetrabutylammonium bromide (1.6 g, 5 mmol). $PhSO_2Cl$ (11.0 g, 62 mmol) in benzene (80 ml) was added to the vigorously stirred mixture and stirring was continued at room temperature for 2 h. After this the benzene layer was separated, washed with water (100 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallized from AcOEt–hexane to give pale yellow prisms (16.1 g, 84%), mp 127–128 °C (lit.,[27] mp 125–127 °C); δ_H(300 MHz; $CDCl_3$–TMS) 7.27–7.60 (6 H, m), 7.71 (1 H, s), 7.85–7.92 (2 H, m) and 7.95–7.98 (1 H, m); ν_{max}(KBr)/cm^{-1}: 1380 and 1175.

3-Phenyl-1-phenylsulfonylindole 7a

According to general procedure C. The crude product obtained using 3-iodo-1-phenylsulfonylindole **6a** (0.76 g, 2 mmol) and iodobenzene (0.40 g, 2 mmol), was purified by silica gel (50 g) column chromatography using AcOEt–hexane (1:9) as eluent and then recrystallized from AcOEt–hexane to give colourless needles (0.55 g, 83%), mp 141–143 °C; δ_H(300 MHz; $CDCl_3$–TMS) 7.25–7.65 (10 H, m), 7.70 (1 H, s), 7.78 (1 H, d, *J* 8), 7.90–7.95 (2 H, m) and 8.70 (1 H, d, *J* 8); $\nu_{max}(CHCl_3)/cm^{-1}$ 1370 and 1180; *m*/*z* 333 (M^+) [Found (HRMS): 333.0819. Calc. for $C_{20}H_{15}NO_2S$: 333.0824].

1-Phenylsulfonyl-3-(2-pyridyl)indole 7b

According to general procedure C. The crude product obtained using 3-iodo-1-phenylsulfonylindole **6a** (0.76 g, 2 mmol) and 2-bromopyridine (0.38 g, 2.4 mmol), was purified by silica gel (30 g) column chromatography using AcOEt–hexane (7:93) as an eluent and then recrystallized from AcOEt–hexane to give colourless needles (0.48 g, 72%), mp 125–126 °C; δ_H(300 MHz; $CDCl_3$–TMS) 7.10–7.60 (6 H, m), 7.65–7.80 (2 H, m), 7.90–7.95 (2 H, m), 8.00–8.10 (2 H, m), 8.33 (1 H, m) and 8.70 (1 H, d, *J* 5), $\nu_{max}(CHCl_3)/cm^{-1}$ 1380 and 1180; *m/z* 334 (M^+) [Found (HRMS): *m/z* 334.0767. Calc. for $C_{19}H_{14}N_2O_2S$: 334.0776] (Found: C, 68.03; H, 4.29; N, 8.30. Calc. for $C_{19}H_{14}N_2O_2S$: C, 68.25; H, 4.22; N, 8.38%).

1-Phenylsulfonyl-3-(3-pyridyl)indole 7c

According to general procedure C. The crude product obtained using 3-iodo-1-phenylsulfonylindole **6a** (0.38 g, 1 mmol) and 3-iodopyridine (0.25 g, 1.2 mmol), was purified by silica gel (10 g) column chromatography using AcOEt–hexane (1:2) and AcOEt–hexane–Et_3N (3:6:1) as eluent. The product obtained from the AcOEt–hexane–Et_3N (3:6:1) eluate was recrystallized from AcOEt–hexane to give pale yellow prisms (0.21 g, 72%), mp 158–159 °C; δ_H(300 MHz; $CDCl_3$–TMS) 7.30–8.00 (11 H, m), 8.08 (1 H, d, *J* 8), 8.61 (1 H, dd, *J* 4.8, 1.5) and 8.87 (1 H, d, *J* 2); ν_{max}(KBr)/cm^{-1} 1370 and 1180; *m/z* 334 (M^+) [Found (HRMS): *m/z* 334.0803. Calc. for $C_{19}H_{14}N_2O_2S$: 334.0776].

1-Phenylsulfonyl-3-thiazol-2-ylindole 7d

According to general procedure C. The crude product obtained using 3-iodo-1-phenylsulfonylindole **6a** (0.38 g, 1 mmol) and 2-iodothiazole (0.25 g, 1.2 mmol), was purified by silica gel (20 g) column chromatography using AcOEt–hexane (15:85) as an eluent to give a pale yellow viscous liquid (0.25 g, 73%), δ_H(300 MHz; $CDCl_3$–TMS) 7.30–7.60 (6 H, m), 7.89–7.97 (3 H, m), 8.00–8.10 (1 H, m), 8.18 (1 H, s) and 8.25–8.30 (1 H, m); *m/z* 340 (M^+) [Found (HRMS): *m/z* 340.0333. Calc. for $C_{17}H_{12}N_2O_2S$: 340.0339].

Camalexin (3-thiazol-2-ylindole)

A mixture of 1-phenylsulfonyl-3-thiazol-2-yl-indole **7d** (0.18 g, 0.53 mmol), 3 M NaOH (2 ml) and MeOH (10 ml) was stirred at room temperature for 4 h. The mixture was diluted with water (10 ml) and extracted with $CHCl_3$ (10 ml × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was purified by silica gel (30 g) column chromatography using AcOEt–hexane (1:9 and 1:3) as eluents. The crude product obtained from the AcOEt–hexane (1:3) eluate was recrystallized from EtOH to give colourless needles (0.166 g, 83%), mp 149–150 °C (lit.,[31] mp 147–148 °C); δ_H(300 MHz; $CDCl_3$–TMS) 7.20–7.50 (4 H, m), 7.80–7.90 (2 H, m), 8.25 (1 H, m) and 8.60 (1 H, br s); *m/z* 200 (M^+) [Found (HRMS): *m/z* 200.0401. Calc. for $C_{11}H_8N_2S$: 200.0408].

Ethyl 3-iodo-1-phenylsulfonylindole-2-carboxylate 6b

To a vigorously stirred mixture of ethyl 3-iodo-2-indolecarboxylate[40] (7.09 g, 22.5 mmol), 50% aq. NaOH (30 ml), water (50 ml) and tetrabutylammonium bromide (1.0 g, 3 mmol) in benzene (50 ml) was added $PhSO_2Cl$ (7.0 g, 40 mmol) in benzene (30 ml). The mixture was stirred at room temperature for 2 h after which the benzene layer was separated and the aqueous layer was extracted with Et_2O (50 ml). The combined organic layer and extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was purified by silica gel (200 g) column chromatography using AcOEt–hexane (1:9) as eluent. The crude product was recrystallized from benzene–hexane to give colourless prisms (9.6 g, 76%), mp 128–130 °C; δ_H(300 MHz; $CDCl_3$–TMS) 1.47 (3 H, t, *J* 7.3), 4.54 (2 H, q, *J* 7.3) and 7.30–8.00 (9 H, m); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725, 1380 and 1195; *m/z* 455 (M^+) (Found: C, 44.61; H, 2.97; N, 3.10. Calc. for $C_{17}H_{14}INO_4S$: C, 44.85; H, 3.10; N, 3.08%).

Ethyl 3-phenyl-1-phenylsulfonylindole-2-carboxylate 13a

According to general procedure C. The crude product obtained using ethyl 3-iodo-1-phenylsulfonylindole-2-carboxylate **6b** (0.46 g, 1 mmol) and iodobenzene (0.41 g, 2 mmol), was purified by silica gel (80 g) column chromatography using AcOEt–hexane (7:93 and 1:9) as eluents. The crude product obtained from the AcOEt–hexane (1:9) eluate was recrystallized from AcOEt–hexane to give colourless prisms (180 mg, 44%), mp 124–125 °C; δ_H(300 MHz; $CDCl_3$–TMS) 1.25 (3 H, t, *J* 7.3), 4.35 (2 H, q, *J* 7.3) and 7.20–8.10 (14 H, m); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1380 and 1195; *m/z* 405 (M^+) [Found (HRMS): *m/z* 405.1046. Calc. for $C_{23}H_{19}NO_4S$: 405.1035] (Found: C, 67.88; H, 4.92; N, 3.51. Calc. for $C_{23}H_{19}NO_4S$: C, 68.13; H, 4.72; N, 3.45%).

Ethyl 1-phenylsulfonyl-3-(2-pyridyl)indole-2-carboxylate 13b

According to general procedure C. The crude product obtained using ethyl 3-iodo-1-phenylsulfonylindole-2-carboxylate **6b** (0.46 g, 1 mmol) and 2-bromopyridine (0.32 g, 2 mmol), was purified by silica gel (40 g) column chromatography using AcOEt–hexane (1:9 and 1:4) as eluents. The crude product obtained from the AcOEt–hexane (1:4) eluate was partitioned between ice-cooled 3 M aq. HCl (30 ml) and Et_2O (30 ml). The HCl extract was separated, made alkaline with Na_2CO_3 and extracted with Et_2O (30 ml × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was recrystallized from AcOEt–hexane to give colourless needles (180 mg, 44%), mp 132–133 °C; δ_H(60 MHz; $CDCl_3$–TMS) 1.34 (3 H, t, *J* 7.3), 4.45 (2 H, q, *J* 7.3), 7.2–8.1 (12 H, m) and 8.69 (1 H, d, *J* 3.0); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1375 and 1195; *m/z* 406 (M^+) [Found (HRMS): *m/z* 406.1011. Calc. for $C_{22}H_{18}N_2O_4S$: 406.0987].

2-Phenyl-1-phenylsulfonylindole 4d

(a) To a solution of diisopropylamine (0.14 ml, 1.05 mmol) in THF (5 ml), was added 1.28 M BuLi (0.82 ml, 1.05 mmol) in hexane at −78 °C under an argon atmosphere, and the mixture was stirred for 1 h. 1-Phenylsulfonylindole **1d** (257 mg, 1.0 mmol) in THF (2 ml) was added to the LDA solution in THF at < −60 °C and the mixture was stirred at −78 °C for 1.5 h; it was then warmed to −20 to 0 °C during 1 h. 1 M $ZnCl_2$ in THF (1.2 ml, 1.2 mmol) was added at −78 °C to the mixture which was then stirred for 30 min. After the mixture had warmed to room temperature for 30 min, a solution of iodobenzene (0.13 ml, 1.2 mmol) and [$Pd(PPh_3)_4$] (0.05 mmol) in THF (1 ml) was added to it and the whole was stirred at room temperature for 30 min; it was then refluxed for 12 h. The reaction mixture was then diluted with water and extracted with CH_2Cl_2 (30 ml × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was purified by silica gel (20 g) column chromatography using Et_2O–hexane (1:4) as eluent. The crude product was recrystallized from Et_2O–hexane to give colourless prisms (0.17 g, 51%).

(b) According to general procedure C. The crude product obtained using 2-iodo-1-phenylsulfonylindole **6b** (0.76 g, 2 mmol) and iodobenzene (0.30 g, 3 mmol) was purified by silica gel (70 g) column chromatography using AcOEt–hexane (7:93). The crude product was recrystallized from MeOH to give colourless prisms (0.38 g, 57%), mp 104–105 °C; δ_H(300 MHz; $CDCl_3$–TMS) 6.55 (1 H, s), 7.20–7.50 (13 H, m) and 8.31 (1 H, d, *J* 8.2); $\nu_{max}(CHCl_3)/cm^{-1}$ 1380 and 1180; *m/z* 333 (M^+) [Found (HRMS): *m/z* 333.0819. Calc. for $C_{20}H_{15}NO_2S$: 333.0824].

1-Phenylsulfonyl-2-(2-pyridyl)indole 8

According to general procedure C. The crude product obtained using 2-iodo-1-phenylsulfonylindole **6b** (0.38 g, 1 mmol) and 2-bromopyridine (0.19 g, 1.2 mmol), was purified by silica gel (20 g) column chromatography using AcOEt–hexane (1:4) as eluent. The crude product was recrystallized from

MeOH to give colourless needles (0.15 g, 45%), mp 118–119 °C (lit.,[35] mp 117–119 °C); δ_H(300 MHz; $CDCl_3$–TMS) 6.88 (1 H, s), 7.20–7.80 (11 H, m), 8.20 (1 H, dd, *J* 0.7, 8.4) and 8.69 (1 H, m); $\nu_{max}(CHCl_3)/cm^{-1}$ 1375 and 1220; *m/z* 334 (M^+) [Found (HRMS): *m/z* 334.0754. Calc. for $C_{19}H_{14}N_2O_2S$: 334.0776].

Methyl 1-phenylsulfonylindole-3-carboxylate

A mixture of 3-iodo-1-phenylsulfonylindole (1.9 g, 5 mmol), CO (6 atm), $Pd(OAc)_2$ (55 mg, 0.25 mmol), Et_3N (0.6 g, 1.2 mmol) and MeOH (50 ml) was heated in a sealed tube at 120 °C for 24 h. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by silica gel (60 g) column chromatography using AcOEt–hexane (1:9 and 3:17) as eluents. The crude product obtained from the AcOEt–hexane (3:17) eluate was recrystallized from AcOEt–hexane to give colourless prisms (1.14 g, 72%), mp 142–143 °C; δ_H(300 MHz; $CDCl_3$–TMS) 3.93 (3 H, s), 7.30–7.70 (5 H, m), 7.90–8.00 (3 H, m), 8.10–8.20 (1 H, m) and 8.29 (1 H, s); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715, 1385 and 1175; *m/z* 315 (M^+) [Found (HRMS): *m/z* 315.0557. Calc. for $C_{16}H_{13}NO_4S$: 315.0564].

Methyl 4-iodo-1-phenylsulfonylindole-3-carboxylate 14

A mixture of methyl 1-phenylsulfonylindole-3-carboxylate (0.95 g, 3 mmol), 0.88 M thallium(III) trifluoroacetate in CF_3CO_2H (5.1 ml, 4.5 mmol) and CF_3CO_2H (3 ml) was stirred at room temperature for 5 h shielded from the light.[41] After evaporation of the mixture to remove the solvent, a mixture of KI (5.0 g, 30 mmol), water (40 ml) and DMF (5 ml) was added to the residue. After being stirred at room temperature for 18 h, the reaction mixture was diluted with MeOH and $CHCl_3$, filtered through a Celite® pad, washed with aq. $Na_2S_2O_3$ and saturated brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallized from AcOEt–hexane to give yellow needles (0.77 g, 58%), mp 167–168 °C; δ_H(300 MHz; $CDCl_3$–TMS) 3.95 (3 H, s), 7.00–7.10 (1 H, m), 7.40–7.70 (3 H, m), 7.80–8.10 (4 H, m) and 8.17 (1 H, s); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720, 1380 and 1180; *m/z* 441 (M^+) [Found (HRMS): *m/z* 440.9562. Calc. for $C_{16}H_{12}INO_4S$: 440.9530].

Methyl 4-phenyl-1-phenylsulfonylindole-3-carboxylate 15

According to general procedure C. The crude product obtained using methyl 4-iodo-1-phenylsulfonylindole-3-carboxylate **14** (0.44 g, 1 mmol) and iodobenzene (0.24 g, 1.2 mmol), was purified by silica gel (80 g) column chromatography using AcOEt–hexane (1:9 and 3:17) as eluents. The crude product obtained from the AcOEt–hexane (3:17) eluate was recrystallized from AcOEt–hexane to give colourless prisms (0.27 g, 43%), mp 164–165 °C; δ_H(300 MHz; $CDCl_3$–TMS) 3.22 (3 H, s), 7.20–7.60 (10 H, m), 7.90–8.00 (3 H, m) and 8.20 (1 H, s); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720, 1380 and 1160; *m/z* 391 (M^+) [Found (HRMS): *m/z* 391.0897. Calc. for $C_{22}H_{17}NO_2S$: 391.0879].

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