Tetrahedron 66 (2010) 6632–6638

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Palladium catalyzed tandem alkenyl- and aryl-C–N bond formation: a cascade N-annulation route to 4-, 5-, 6- and 7-chloroindoles

Luke C. Henderson [a,†], Matthew J. Lindon [b], Michael C. Willis [a,*]

[a] Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK
[b] Medicinal Chemistry, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, UK

ARTICLE INFO

Article history:
Received 4 March 2010
Received in revised form 10 May 2010
Accepted 13 May 2010
Available online 20 May 2010

Keywords:
Palladium
Indole
Amination

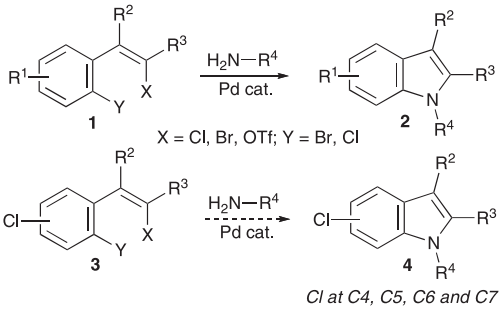
ABSTRACT

A series of trihalogenated alkenylbenzenes undergo consecutive palladium catalyzed inter- and intramolecular amination reactions to deliver a series of 1-functionalized mono-chloroindoles. 4-, 5-, 6- and 7-Chloroindoles can all be prepared; carbamates, anilines and amines can be employed as the *N*-nucleophile.

1. Introduction

Indole heterocycles are embedded in a diverse range of natural products and medicinal agents. The structural variety of indole targets has resulted in an extensive collection of methods for their preparation,[1] including many based on transition-metal catalysis.[2] A valuable sub-set of these transition-metal catalyzed processes is transformations that are used to functionalize an already intact indole core.[3] Although the number of reports of the direct metal catalyzed functionalisation of C–H bonds in indoles, particularly for the C-2 and C-3 positions, is rapidly growing,[4,5] the most general class of substrates for metal catalyzed functionalisation is halogenated indoles. A corollary of this is the need for efficient routes to halogenated indoles. Although the preparation of C-3 halogenated indoles is usually straightforward, access to the remaining halogenated isomers is more challenging.[1c,6]

We have recently demonstrated that a broad range of 2-(2-haloalkenyl)-aryl halides,[7] as well as the corresponding alkenyl triflates,[8] can undergo two sequential palladium catalyzed amination reactions—the first intermolecular, the second intramolecular—to provide efficient routes to a variety of *N*-functionalised indoles (**1**→**2**, Scheme 1).[9] With aryl chlorides now established as useful substrates in a wide range of transition-metal catalyzed reactions,[10] we instigated a study to adapt our annulative indole syntheses to target chloro-substituted indoles. In this report we document the realisation of this goal, and show that with the appropriate choice of halogen substituents, trihalogenated substrates can be efficiently transformed into the corresponding mono-chloroindoles (**3**→**4**, Scheme 1).



Scheme 1. Tandem palladium-catalyzed amination routes to 1-functionalised indoles and chloroindoles.

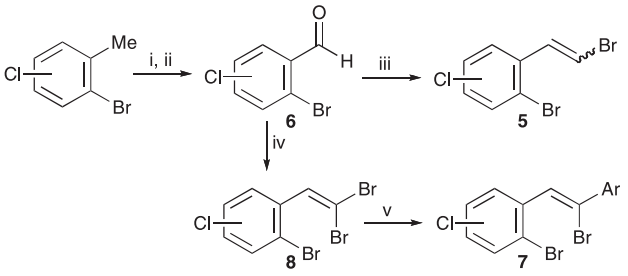
2. Results and discussion

One key advantage of the approach to chlorinated indoles described in Scheme 1 is the ready availability of suitable halogenated substrates. For example, substrates with no substituents on the alkene (corresponding to the C-2 and C-3 positions in the indole products, **5** Scheme 2) are available by a straightforward Wittig

* Corresponding author. Tel.: +44 1865 285126; fax: +44 1865 285002; e-mail address: michael.willis@chem.ox.ac.uk (M.C. Willis).
† Present address: School of Life and Environmental Sciences, Deakin University, Pigdons Road, Geelong, Australia.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.05.046

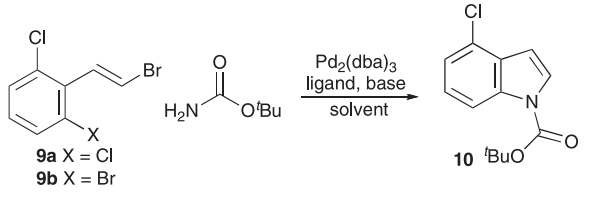
reaction on the corresponding aldehydes **6**. Substrates bearing substituents at what will become C-2 of the indole products, **7** are available from the corresponding 1,1-dibromo-derivatives **8** using Suzuki chemistry; the simple aldehydes are again the key starting materials. All of the mono-chlorinated isomers of *ortho*-bromobenzaldehyde are either commercially available, or accessible using a bromination/oxidation sequence from the related toluene.[11]



Scheme 2. The preparation of the tri- and tetrahalogenated starting materials. Reagents: (i) NBS, AIBN, CCl_4; (ii) NMO, MeCN; (iii) $[Ph_3PCH_2Br]Br$, ^tBuOK; (iv) CBr_4, PPh_3, CH_2Cl_2; (v) $Pd_2(dba)_3$, P(2-furyl)$_3$, Na_2CO_3, Ar-B$(OH)_2$.

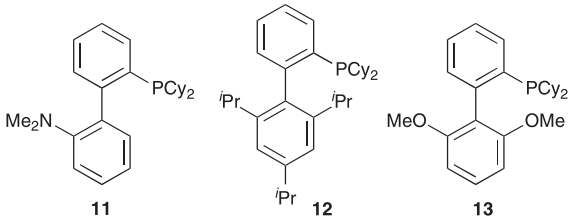
We elected to employ the coupling of 1,3-dihalo-(2-bromovinyl) benzenes **9** and *tert*-butyl carbamate as a test platform to evaluate suitable catalysts (Table 1). Initial reaction conditions were based on precedent from our earlier studies; reaction of dichloro substrate **9a** using ligand **11** and Cs_2CO_3 in toluene at 110 °C delivered the desired indole **10** in a poor yield of 17% as the only product (entry 1, Table 1). We attributed the poor mass balance to thermal degradation of the styrene starting material under the reaction conditions. We hoped that by moving to the bromo-chloro substrate **9b** we could achieve a faster reaction and limit decomposition; reaction of substrate **9b** at the lower temperature of 85 °C using DME as solvent delivered the expected indole in 37% yield (entry 2). The remainder of the optimization study employed the bromo-chloro substrate, and explored variation of biphenyl ligand (**11**, **12** or **13**),[12] base (Cs_2CO_3, K_2CO_3 or K_3PO_4) and reaction temperature (Table 1). The optimized conditions involved using the dimethoxy-substituted biphenyl ligand (**13**) in combination with Cs_2CO_3 in toluene at 110 °C (entry 7).

Table 1
Evaluation of reaction conditions for the formation of 4-chloroindole **10**[a]



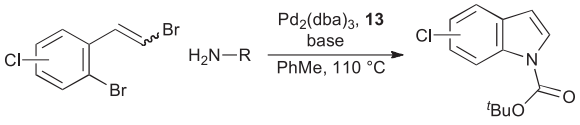
Entry	X	Ligand	Base	Solvent	Temp (°C)	Yield[b] (%)
1	Cl	**11**	Cs_2CO_3	PhMe	110	17
2	Br	**11**	Cs_2CO_3	DME	85	37
3	Br	**12**	Cs_2CO_3	PhMe	85	38
4	Br	**12**	K_2CO_3	PhMe	110	<5
5	Br	**12**	K_3PO_4	DME	85	15
6	Br	**12**	Cs_2CO_3	PhMe	110	41
7	Br	**13**	Cs_2CO_3	PhMe	110	66
8	Br	**13**	Cs_2CO_3	Xylene	130	24

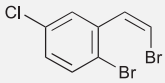
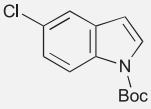
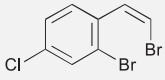
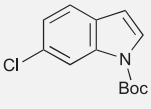
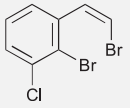
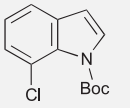
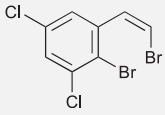
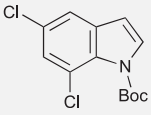
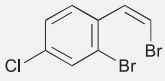
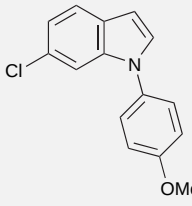
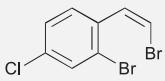
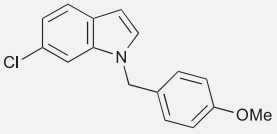
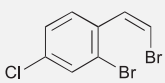
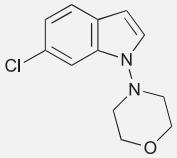
[a] Dihalo substrates **9a** and **9b** used as a >20:1 *E:Z* mix of isomers. Conditions: $Pd_2(dba)_3$ (2.5 mol %), ligand (7.5 mol %), base (2.5 equiv), *tert*-butyl carbamate (1.05 equiv), 16 h.
[b] Isolated yields.



With an efficient set of conditions to access the 4-chloroindole derivative secured, we next applied the optimized conditions to the remaining isomers of the starting materials (Table 2). Entries 1–3 demonstrate the efficient preparation of the 5-, 6- and 7-chloro

Table 2
The preparation of 5-, 6- and 7-chloroindole derivatives, and variation of the *N*-coupling partner[a]



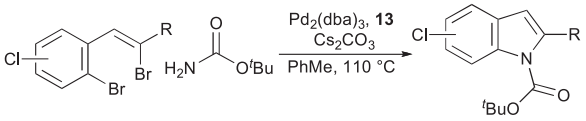
Entry	Substrate	Product	Yield[b] (%)
1[c]			69
2[d]			84
3[e]			68
4[f]			39
5[d,g]			87
6[d,g]			67
7[d,g]			68

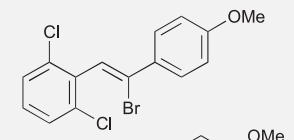
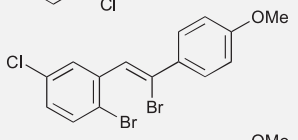
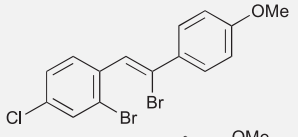
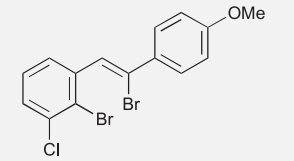
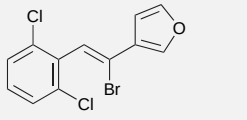
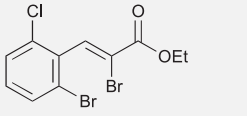
[a] Conditions: $Pd_2(dba)_3$ (2.5 mol %), ligand **13** (7.5 mol %), Cs_2CO_3 (2.5 equiv), *N*-nucleophile (1.05 equiv), toluene 110 °C, 16 h.
[b] Isolated yields.
[c] *E:Z* 1:9.
[d] *E:Z* 1:9.
[e] *E:Z* 1:8.
[f] *E:Z* 1:9.
[g] NaO^{t}Bu used as base.

derivatives, while entry 4 illustrates that access to dichlorinated products (5,7-dichloroindole in this example) is also possible. All of the indole forming reactions discussed so far have featured *tert*-butyl carbamate as the *N*-nucleophile, resulting in the formation of *N*-Boc indoles; in order to assess whether different substituents could be installed, we next evaluated a number of alternative *N*-coupling partners. Combining the 6-chloroindole precursor with *p*-anisidine using the conditions optimized for the carbamate coupling produced none of the expected indole product, returning only starting materials. However, if the base was switched from caesium carbonate to sodium *tert*-butoxide, then the desired *N*-aryl indole was obtained in 87% yield (entry 5). Using the stronger base also allowed an alkylamine (*p*-methoxybenzylamine), and an *N*,*N*-dialkylhydrazine (*N*-aminomorpholine) to be employed as coupling partners (entries 6 and 7).

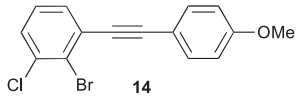
The final variation explored was extension of the chemistry to allow the formation of C-1 substituted indole products. As shown in Scheme 2, a variety of aryl-substituted substrates were readily accessible using Suzuki chemistry; a 4-methoxyphenyl group was used as a standard substituent to allow the regioisomeric chloro-substrates to be evaluated. Employing *tert*-butyl carbamate as the *N*-coupling partner allowed the original caesium carbonate reaction conditions to be employed (Table 3). When the 4-chloro substrate was subjected to the standard reaction conditions the desired indole was obtained in a disappointing 34% yield. However, exchanging the ligand to the tri-isopropyl variant, **12**, and using DME as solvent allowed the expected 4-chloroindole to be isolated in an encouraging 71% yield (entry 1). The combination of ligand **12** and DME was used as standard for substrates featuring alkenyl-substituents. Entries 2 and 3 illustrate that both the 5-Cl, and 6-Cl isomers were readily accessible using the established conditions. When the 7-chloro substrate was subjected to the reaction conditions none of the desired indole was obtained; however, the corresponding alkyne (**14**), resulting from elimination of HBr, was isolated in 78% yield (entry 4). A further coupling of the same substrate but employing the less sterically demanding ethyl-carbamate was similarly unsuccessful (73% of the alkyne isolated). The final two examples serve to demonstrate that alternative C-2 groups can also be incorporated, with both a 3-furyl, and an ethyl ester substituent being successfully incorporated. The ester substituent was introduced into the substrate using a Br-substituted Horner/Wadsworth/Emmons olefination reaction on the corresponding aldehyde.

Table 3
The preparation of C-2 functionalised mono-chloroindoles[a]



Entry	Substrate	Yield[b] (%)
1		71
2		75
3		81
4[c]		0
5		61
6		61

[a] Conditions: **5a** (1.0 equiv), amine (2.0 equiv), $Pd(OAc)_2$ (5 mol %), ligand (12 mol %), Cs_2CO_3 (2.2 equiv), toluene, 110 °C, 6 h. Substrate **5a** was used as a >20:1 mixture of *Z*/*E* isomers.
[b] Isolated yields.
[c] Alkyne **14** isolated in 78% yield.



14

3. Conclusion

We have established that a cascade palladium catalysed inter/intramolecular amination process can be applied to trihalogenated alkenylbenzenes to allow access to synthetically useful mono-chloroindole derivatives. The approach removes the issue of selective chlorination of indole derivatives, to that of the preparation of suitably halogenated benzene derivatives. The strategy allows the ready preparation of 4-, 5-, 6- and 7-chlorinated indoles.

4. Experimental section

4.1. General information

All reactions were performed under an inert atmosphere of nitrogen, in oven dried glassware. Palladium catalysts and ligands were purchased from Aldrich Chemical Company or Strem Chemical. *tert*-Butyl 4-chloro-1*H*-indole-1-carboxylate (**10**, Table 1, entry 7),[13] *tert*-butyl 5-chloro-1*H*-indole-1-carboxylate (Table 2, entry 1),[13] *tert*-butyl 6-chloro-1*H*-indole-1-carboxylate (Table 2, entry 2)[14] and *tert*-butyl 7-chloro-1*H*-indole-1-carboxylate (Table 2, entry 3)[14] are known compounds and as such data is not included below.

4.2. General procedure (A) for the Wittig derived synthesis of vinyl bromide substrates; exemplified by the preparation of 1-bromo-2-[(*E*)-2-bromovinyl]-3-chlorobenzene (Table 1, entry 2 substrate)

Potassium *tert*-butoxide (560 mg, 5.0 mmol) was added to a suspension of (methylbromo)triphenylphosphonium bromide (2.2 g, 5.0 mmol) in THF (25 mL) cooled to −78 °C and the suspension stirred for 40 min. 2-Bromo-6-chlorobenzaldehyde (1.0 g, 4.6 mmol) was added as a solid to the suspension and the reaction slowly warmed to room temperature over 12 h. The crude product was poured into petrol (100 mL), filtered through Celite and the Celite washed repeatedly with petrol (3×50 mL). The crude

solution was reduced in vacuo to give a pale yellow solid, which was purified by flash chromatography (SiO_2, 25% petrol/hexane) to give the *vinyl bromide* as a white crystalline solid (604 mg, 30%, *E*:*Z*>20:1); mp 40–42 °C; ν_{max} (thin film, cm^{-1}) 3080, 2962, 1473, 897; ^1H NMR (400 MHz, $CDCl_3$) 7.52 (dd, *J*=8.0, 1.2 Hz, 1H), 7.38 (dd, *J*=8.0, 1.2 Hz, 1H), 7.12 (d, *J*=14.2 Hz, 1H), 7.08 (dd, *J*=8.0, 8.0 Hz, 1H), 6.88 (d, *J*=14.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), 134.6, 133.8, 132.7, 131.7, 129.3, 129.2, 123.9, 114.5; MS (FI^+) 296, 298, 294; HRMS for $C_8H_5{}^{79}Br^{81}Br^{35}Cl$ predicted 293.8447, found 293.8447.

4.2.1. 1-Bromo-2-[(Z)-2-bromovinyl]-4-chlorobenzene (Table 2, entry 1 substrate). Prepared and purified according to General procedure A, using 2-bromo-5-chlorobenzaldehyde[11] (0.50 g, 2.30 mmol), potassium *tert*-butoxide (307 mg, 2.30 mmol) and (methylbromo) triphenylphosphonium bromide (1.20 g, 2.74 mmol) to give the *vinyl bromide* as a clear oil (376 mg, 56%, *E*/*Z* 1:9); ν_{max} (thin film/cm^{-1}) 3083, 2977, 2866, 1547, 1581, 1319, 1038; ^1H NMR (400 MHz, $CDCl_3$) 7.77 (d, *J*=2.4 Hz, 1H), 7.53 (d, *J*=8.4 Hz, 1H), 7.18 (dd, *J*=8.4, 2.4 Hz, 1H), 7.14 (d, *J*=8.0 Hz, 1H), 6.65 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 136.5, 133.6, 131.3, 130.2, 129.5, 126.9, 121.5, 110.6; MS (EI^+) 296, 294, 298; HRMS for $C_8H_5{}^{79}Br^{81}Br^{35}Cl$ predicted 293.8447, found 293.8441.

4.2.2. 1-Bromo-2-[(Z)-2-bromovinyl]-5-chlorobenzene (Table 2, entry 2 substrate). Prepared using General procedure A, employing 2-bromo-4-chlorobenzaldehyde[15] (0.50 g, 2.30 mmol), potassium *tert*-butoxide (307 mg, 2.74 mmol) and (methylbromo)triphenylphosphonium bromide (1.20 g, 2.74 mmol) to give the *vinyl bromide* as a white solid (367 mg, 55%, *E*/*Z* 1:9); mp 44–46 °C; ν_{max} (thin film/cm^{-1}) 3081, 2979, 2866, 1540, 1582, 1316; ^1H NMR (200 MHz, $CDCl_3$) 7.73 (d, *J*=8.4 Hz, 1H), 7.63 (d, *J*=2.2 Hz, 1H), 7.33 (dd, *J*=8.4, 2.2 Hz, 1H), 7.15 (d, *J*=8.2 Hz, 1H), 6.62 (d, *J*=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 134.5, 133.6, 132.3, 131.3, 131.1, 127.2, 124.0, 110.0; MS (FI^+) 296, 298, 294; HRMS for $C_8H_5{}^{79}Br^{81}Br^{35}Cl$ predicted 293.8447, found 293.8456.

4.2.3. 1-Bromo-2-[(Z)-2-bromovinyl]-6-chlorobenzene (Table 2, entry 3 substrate). Prepared using General procedure A, employing 2-bromo3-chlorobenzaldehyde (410 mg, 1.88 mmol), potassium *tert*-butoxide (255 mg, 2.30 mmol) and (methylbromo)triphenylphosphonium bromide (1 g, 2.30 mmol) to give the *vinyl bromide* as a clear oil (34 mg, 68%, *E*:*Z* 1:8); ν_{max} (thin film/cm^{-1}); 3086, 2978, 2866, 1541, 1577, 1316; ^1H NMR (400 MHz, $CDCl_3$) 7.60 (dd, *J*=8.0, 1.2 Hz, 1H), 7.45 (dd, *J*=8.0, 1.2 Hz, 1H), 7.29 (dd, *J*=8.0, 8.0 Hz, 1H), 7.20 (d, *J*=8.0 Hz, 1H), 6.63 (d, *J*=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 137.7, 135.2, 132.7, 129.8, 128.6, 127.6, 123.6, 110.1; MS (EI^+) 296; Predicted for $C_8H_5{}^{79}Br^{81}Br^{35}Cl$ 293.8447, found 293.8443.

4.2.4. 1-Bromo-2-[(Z)-2-bromovinyl]-4,6-dichlorobenzene (Table 2, entry 4 substrate). Prepared using General procedure A, employing 2-bromo-3,5-dichlorobenzaldehyde[16] (134 mg, 0.53 mmol), potassium *tert*-butoxide (65 mg, 0.58 mmol) and (methylbromo)triphenylphosphonium bromide (253 mg, 0.58 mmol) to give the *vinyl bromide* as a white solid (98 mg, 56%, *E*:*Z* 1:9); mp 40–41 °C; ν_{max} (thin film/cm^{-1}) 3076, 3016, 2920, 1612, 1566, 1399, 1386, 1313, 1174, 1030, 918, 819, 722, 674; ^1H NMR (200 MHz, $CDCl_3$) 7.59 (d, *J*=2.2 Hz, 1H), 7.46 (d, *J*=2.2 Hz, 1H), 7.14 (d, *J*=8.0 Hz, 1H), 6.67 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.6, 136.0, 133.1, 131.8, 129.4, 128.6, 121.9, 111.3; MS (EI^+) 330, 332, 328; HRMS (EI^+) predicted for $C_8H_4{}^{79}Br^{79}Br^{35}Cl^{35}Cl$ 327.8057, found 327.8057.

4.3. General procedure (B) for indole formation using non-substituted substrates; exemplified by the preparation of *tert*-butyl 4-chloro-1*H*-indole-1-carboxylate (10, Table 1, entry 7)[13]

Toluene (0.68 mL) was added to a flask charged with $Pd_2(dba)_3$ (7.7 mg, 8.5 μmol), Cs_2CO_3 (273 mg, 8.5 mmol), ligand **13** (10.5 mg, 25.5 μmol) and alkene **9b** (100 mg, 0.34 mmol) and the solution was heated to 110 °C for 16 h. The solution was allowed to cool to room temperature then filtered through a Celite pad, followed by repeated washing of the Celite with DCM (3×50 mL). The filtrate was then reduced to dryness under reduced pressure. The crude product was purified via flash chromatography (SiO_2, 5% Et_2O/petrol) to give the *indole* as a yellow oil (56 mg, 66%); ν_{max} (thin film/cm^{-1}) 3155, 3122, 2980, 2933, 1744, 1531, 1474, 1426, 1345, 1148; ^1H NMR (400 MHz, $CDCl_3$) 8.07 (dd, *J*=8.6, 8.6 Hz, 1H), 7.64 (d, *J*=3.8 Hz, 1H), 7.24 (m, 2H), 6.70 (d, *J*=3.8 Hz, 1H), 1.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.4, 132.7, 129.2, 126.4, 126.0, 124.8, 122.4, 113.7, 105.3, 84.2, 28.1; MS (FI^+) 251, 253; HRMS (FI^+) predicted for $C_{13}H_{14}{}^{35}ClO_2$ 251.0716, found 251.0713.

4.3.1. tert-Butyl 5,7-dichloro-1H-indole-1-carboxylate (Table 2, entry 4). Prepared using General procedure B, employing 1-bromo-2-[(*Z*)-2-bromovinyl]-4,6-dichlorobenzene (98 mg, 0.3 mmol), ligand **13** (9.2 mg, 22.5 μmol), caesium carbonate (244 mg, 0.75 mmol), $Pd_2(dba)_3$ (6.9 mg, 7.5 μmol) and *tert*-butyl carbamate (39 mg, 0.33 mmol) to give the *indole* as a yellow oil (33 mg, 39%); ν_{max} (thin film/cm^{-1}) 2930, 1759, 1739, 1448, 1319, 1152; ^1H NMR (400 MHz, $CDCl_3$) 7.58 (d, *J*=3.6 Hz, 1H), 7.46 (d, *J*=1.8 Hz, 1H), 7.33 (d, *J*=1.8 Hz, 1H), 6.52 (d, *J*=3.6 Hz, 1H), 1.66 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 148.4, 134.6, 130.67, 130.64, 128.5, 126.1, 120.9, 119.2, 106.3, 84.8, 27.9; MS (ESI^+) 308, 310; HRMS (ESI^+) predicted for $C_{13}H_{13}N^{35}Cl^{35}ClNaO_2$ 308.0213, found 308.0216.

4.3.2. 6-Chloro-1-(4-methoxyphenyl)-1H-indole (Table 2, entry 5). Prepared using General procedure B, employing 1-bromo-2-[(*Z*)-2-bromovinyl]-5-chlorobenzene (0.10 mg, 0.34 mmol), sodium *tert*-butoxide (82 mg, 0.85 mmol), Pd_2dba_3 (10.5 mg, 8.5 μmol), ligand **13** (7.7 mg, 25.5 μmol) and *p*-methoxyaniline (46 mg, 0.37 mmol) in toluene (0.68 mL) to give the *indole* as a yellow solid after purification by flash chromatography (SiO_2, 5% Et_2O/petrol), (76 mg, 87%); mp 49–51 °C; ν_{max} (thin film/cm^{-1}) 3001, 2932, 2835, 1517, 1463, 1249; ^1H NMR (400 MHz, $CDCl_3$), 7.60 (d, *J*=8.4 Hz, 1H), 7.45 (d, *J*=1.6 Hz, 1H), 7.39 (d, *J*=9.2 Hz, 2H), 7.28 (d, *J*=3.2 Hz, 1H), 7.15 (dd, *J*=8.4, 1.6 Hz, 1H), 7.07 (d, *J*=9.2 Hz, 2H), 6.64 (d, *J*=3.2 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 158.5, 136.7, 132.1, 129.0, 128.1, 127.4, 126.0, 121.8, 120.7, 114.8, 110.3, 102.9, 55.6; MS (CI^+) 258, 260; HRMS (CI^+) predicted for $C_{15}H_{13}NO^{35}Cl$ 258.0686, found 258.0688.

4.3.3. 6-Chloro-1-(4-methoxybenzyl)-1H-indole (Table 2, entry 6). Prepared using General procedure B, employing 1-bromo-2-[(*Z*)-2-bromovinyl]-5-chlorobenzene (100 mg, 0.34 mmol), sodium *tert*-butoxide (82 mg, 0.85 mmol), *p*-methoxybenzyl amine (51 mg, 0.37 mmol), Pd_2dba_3 (7.7 mg, 25.5 μmol) and ligand **13** (10.5 mg, 8.5 μmol) in toluene (0.68 mL) to give the desired *indole* as a pale yellow oil after flash chromatography (SiO_2, 5% Et_2O/petrol), (66 mg, 68%); ν_{max} (thin film/cm^{-1}) 2930, 2835, 1611, 1512, 1463, 1248, 804; ^1H NMR (400 MHz, $CDCl_3$) 7.56 (d, *J*=8.4 Hz, 1H), 7.31 (br s, 1H), 7.11–7.06 (m, 4H), 6.86 (d, *J*=8.8 Hz, 2H), 6.53 (d, *J*=3.2 Hz, 1H), 5.21 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.2, 136.6, 128.9, 128.8, 128.2, 127.6, 127.2, 121.8, 120.2, 114.2, 109.7, 101.7, 55.3, 49.7; MS (FI^+) 271, 273; HRMS (FI^+) predicted for $C_{16}H_{14}NO^{35}Cl$ 271.0770, found 271.0764.

4.3.4. Chloro-1-morpholin-4-yl-1H-indole (Table 2, entry 7). Prepared using General procedure B, 1-bromo-2-[(*Z*)-2-bromovinyl]-5-chlorobenzene (100 mg, 0.34 mmol), sodium *tert*-butoxide (82 mg, 0.85 mmol), Pd_2dba_3 (10.5 mg, 8.5 μmol), ligand **13** (7.7 mg, 25.5 μmol) and *N*-aminomorpholine (38 mg, 0.37 mmol) in toluene (0.68 mL) to give the *indole* as colourless crystals after purification via flash chromatography (SiO_2, 10% Et_2O/petrol), (54 mg, 67%); mp

182–184 °C; ν_{max} (thin film/cm^{-1}) 2916, 2850, 1458, 1113, 902; ^{1}H NMR (400 MHz, $CDCl_3$) 7.59 (d, J=2.0 Hz, 1H), 7.50 (d, J=8.2 Hz, 1H), 7.41 (d, J=3.4 Hz, 1H), 7.09 (dd, J=8.2, 2.0 Hz, 1H), 6.50 (d, J=3.4 Hz, 1H), 3.94 (t, J=4.6 Hz, 4H), 3.16 (t, J=4.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 135.4, 128.2, 123.8, 121.9, 121.7, 120.7, 109.6, 101.1, 67.2, 55.5; MS (CI$^+$) 237, 239; HRMS (CI$^+$) predicted for $C_{12}H_{14}N_2O^{35}Cl$ 237.0795, found 237.0793.

4.4. General procedure (C) for the preparation of 1,1-dibromoalkenes; exemplified by the preparation of 1-bromo-4-chloro-2-(2,2-dibromovinyl)benzene

Carbon tetrabromide (2.5 g, 7.2 mmol) was added to a solution of triphenylphosphine (4.0 g, 15.2 mmol) in DCM (30 mL) cooled to 0 °C and the solution was stirred for 40 min. 2-Bromo-5-chlorobenzaldehyde (1.0 g, 4.6 mmol) was added as a solid and the resulting suspension stirred at 0 °C for 3 h. Petrol (200 mL) was added and the suspension filtered through Celite, the Celite was washed with petrol (3×50 mL) and the filtrate was reduced to dryness in vacuo to give a yellow solid. The crude product was purified via flash chromatography (SiO_2, petrol) to give the *gem-dibromide* as a colourless solid (977 g, 58%); mp 74–76 °C; ν_{max} (thin film/cm^{-1}) 3086, 3015, 1889, 1623, 1452, 1387, 1095, 1031; ^{1}H NMR (400 MHz, $CDCl_3$), 7.59 (d, J=2.4 Hz, 1H), 7.52 (d, J=8.8 Hz, 1H), 7.45 (s, 1H), 7.20 (dd, J=8.8, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 137.4, 135.4, 133.7, 133.2, 130.2, 129.8, 120.9, 94.3; MS (FI$^+$) 375, 373, 377, 371; HRMS (FI$^+$) predicted for $C_8H_4{}^{79}Br^{79}Br^{79}Br^{35}Cl$ 371.7552, found 371.7560.

4.4.1. 1-Bromo-5-chloro-2-(2,2-dibromovinyl)benzene. Prepared using General procedure C, employing 2-bromo-4-chlorobenzaldehyde (0.5 g, 2.3 mmol), carbon tetrabromide (1.26 g, 3.8 mmol) and triphenylphosphine (2 g, 7.50 mmol) to give the *gem-dibromide* as a white solid (705 g, 83%); mp 70–71 °C; ν_{max} (thin film/cm^{-1}) 3018, 3066, 1733, 1593, 1578, 1550, 1464, 1374, 1139, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) 7.61 (d, J=2.0 Hz, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.46 (s, 1H), 7.33 (dd, J=8.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), 135.6, 134.9. 134.5, 132.3, 131.0, 127.5, 123.4, 93.6; m/z (FI$^+$) 375, 373, 377, 371; HRMS (FI$^+$) predicted for $C_8H_4{}^{79}Br^{79}Br^{79}Br^{35}Cl$ 371.7552, found 371.7545.

4.4.2. 1-Bromo-6-chloro-2-(2,2-dibromovinyl)benzene. Prepared using General procedure C, employing 2-bromo-3-chlorobenzaldehyde (0.50 g, 2.3 mmol), carbon tetrabromide (1.25 g, 3.77 mmol) and triphenylphosphine (1.97 g, 7.52 mmol) to give the *gem-dibromide* as a white solid (0.74 mg, 86%); mp 71–73 °C; ν_{max} (thin film/cm^{-1}) 3019, 1589, 1445, 197, 1150, 824; ^{1}H NMR (400 MHz, $CDCl_3$) 7.50 (s, 1H), 7.45 (m, 2H), 7.29 (app. t, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.6, 136.8, 135.3, 130.0, 128.5, 127.9, 123.1, 93.9; MS (EI$^+$) 375; HRMS (EI$^+$) predicted for $C_8H_4{}^{79}Br^{79}Br^{79}Br^{35}Cl$ 371.7552, found 371.7562.

4.5. General procedure (D) for the preparation of aryl-substituted substrates using Suzuki chemistry; exemplified by the preparation of 2-[(*Z*)-2-bromo-2-(4-methoxyphenyl) vinyl]-1,3-dichlorobenzene (Table 3, entry 1 substrate)

DME (15 mL) was added to a flask containing $Pd_2(dba)_3$ (68 mg, 75 μmol), tri(2-furyl)phosphine (105 mg, 0.45 mmol), *p*-methoxyphenylboronic acid (502 mg, 3.33 mmol) and 1,3-dichloro-2-(2, 2-dibromovinyl)benzene (1.0 g, 3.0 mmol). The suspension was stirred for 10 min at room temperature then aqueous sodium carbonate (1 M, 6.0 mL, 6.0 mmol) was added and the solution heated to 70 °C for 4 h. The solution was then cooled to room temperature and water (50 mL) was added, and the aqueous phase then extracted with ether (3×20 mL). The combined organic phases were then washed with brine (2×20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was obtained as a yellow oil and purified by flash chromatography (SiO_2, 5% ether/petrol) to give the *vinyl bromide* as a yellow solid (720 mg, 61 %); mp 71–73 °C; ν_{max} (thin film/cm^{-1}) 2933, 2835, 1605, 1575, 1427, 1249, 1175, 773; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.69 (d, J=8.8 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.24 (dd, J=8.0, 8.0 Hz, 1H), 7.02 (s, 1H), 6.94 (d, J=8.8, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.5, 135.7, 134.9, 133.4, 131.5, 131.0, 129.3, 127.9, 123.9, 113.7, 55.5; MS (ES$^+$) 277, 357, 359, 361; HRMS (ES$^+$) predicted for $C_{15}H_{12}{}^{79}Br^{35}Cl^{35}ClO$ 356.9449, found 356.9455.

4.5.1. 1-Bromo-2-[(Z)-2-bromo-2-(4-methoxyphenyl)vinyl]-4-chlorobenzene (Table 3, entry 2 substrate). Prepared using General procedure D, employing 1-bromo-4-chloro-2-(2,2-dibromovinyl) benzene (500 mg, 1.3 mmol), *p*-methoxyphenylboronic acid (207 mg, 1.37 mmol), tri(2-furylphosphine) (46 mg, 0.195 mmol), $Pd_2(dba)_3$ (30 mg, 33 μmol) and sodium carbonate (2.6 mL, 2.6 mmol) to give the *vinyl bromide* (288 mg, 55%); mp 86–87 °C; ν_{max} (thin film/cm^{-1}) 2957, 2927, 2835, 1603, 1507, 1454, 1178, 1030, 810; ^{1}H NMR (400 MHz, $CDCl_3$) 7.77 (d, J=2.2 Hz, 1H), 7.65 (d, J=9.0 Hz, 2H), 7.55 (d, J=8.5 Hz, 1H), 7.17 (dd, J=8.5, 2.2 Hz, 1H), 7.10 (s, 1H), 6.94 (d, J=9.0 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.5, 138.7, 133.4, 132.9, 132.2, 130.9, 129.3, 129.1, 127.9, 126.6, 122.0, 113.7, 55.4; MS (FI$^+$) 402, 400, 404; HRMS (FI$^+$) predicted for $C_{15}H_{11}{}^{79}Br^{35}Cl^{35}Cl$ 399.8865, found 399.8868.

4.5.2. 1-Bromo-2-[(Z)-2-bromo-2-(4-methoxyphenyl)vinyl]-5-chlorobenzene (Table 3, entry 3 substrate). Prepared using General procedure D, employing 1-bromo-5-chloro-2-(2,2-dibromovinyl) benzene (214 mg, 0.65 mmol), tri(2-furyl)phosphine (23 mg, 0.1 mmol), Pd_2dba_3 (15 mg, 16.2 μmol) and *p*-methoxyphenylboronic acid (103 mg, 0.68 mmol) to give the *vinyl bromide* (142 mg, 55%); mp 76–77 °C, ν_{max}(thin film/cm^{-1}) 2931, 2835, 1602, 1506, 1458, 1251, 1173, 1026, 820; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.72 (d, J=8.4 Hz, 1H), 7.66–7.63 (m, 3H), 7.35 (dd, J=8.4, 2.4 Hz, 1H), 7.11 (s, 1H), 6.94 (d, J=8.4 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,) 160.5, 135.7, 134.0, 132.3, 132.0, 131.7, 129.2, 127.4, 127.2, 126.7, 124.5, 113.7, 55.4; MS (FI$^+$) 402, 404, 400; HRMS (FI$^+$) predicted for $C_{15}H_{11}{}^{79}Br^{79}Br^{35}ClO$ 399.8865, found 399.8869.

4.5.3. 1-Bromo-2-[(Z)-2-bromo-2-(4-methoxyphenyl)vinyl]-6-chlorobenzene (Table 3, entry 4 substrate). Prepared using General procedure D, employing 1-bromo-6-chloro-2-(2,2-dibromovinyl) benzene (200 mg, 0.533 mmol), *p*-methoxyphenylboronic acid (89 mg, 0.587 mmol), sodium carbonate (1 M, 1.07 mL, 1.07 mmol), tri(2-furyl) phosphine (18.6 mg, 80 μmol) and $Pd_2(dba)_3$ (12 mg, 13.3 μmol) to give the *vinyl bromide* a white solid (111 mg, 52%); mp; 92–93 °C; ν_{max} (thin film/cm^{-1}) 2993, 2932, 2834, 1508, 1284, 1172, 1030, 819; ^{1}H NMR (400 MHz, $CDCl_3$) 7.66 (d, J=8.0 Hz, 2H), 7.61 (dd, J=8.0, 1.0 Hz, 1H), 7.44 (dd, J=8.0, 1.0 Hz, 1H), 7.31 (app. t, J=8.0 Hz, 1H), 7.17 (s, 1H), 6.94 (d, J=8.0, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.5, 147.5, 140.0, 135.0, 132.2, 129.4, 129.3, 129.2, 128.0, 127.6, 127.5, 113.8, 55.5; MS (CI$^+$) 322; HRMS predicted for $C_{15}H_{11}{}^{79}Br^{79}Br^{35}ClO$ 399.8865, found 399.8856.

4.5.4. 3-[(Z)-1-Bromo-2-(2,6-dichlorophenyl)vinyl]furan (Table 3, entry 5 substrate). Prepared using General procedure D, employing 1,3-dichloro-2-(2,2-dibromovinyl)benzene (0.5 g, 1.5 mmol), tri(2-furyl) phosphine (123 mg, 53 mmol), furan-3-boronic acid (176 mg, 1.59 mmol), $Pd_2(dba)_3$ (35 mg, 38 μmol) and sodium carbonate (1 M, 3.0 mL) to give the *furan* as a yellow oil (326 mg, 68%); ν_{max} (thin film/cm^{-1}) 2925, 1557, 1387, 1164, 790, 774; ^{1}H NMR (400 MHz, $CDCl_3$) 7.76 (m, 1H), 7.50 (m, 1H), 7.38 (d, J=8.4 Hz, 2H), 7.24 (dd, J=8.4 Hz, 1H), 7.05 (s, 1H), 6.73 (dd, J=2.0, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 144.1, 143.5, 135.0, 129.4, 127.9, 127.5, 126.2,

122.9, 120.6, 108.1; MS (ESI^-) 316, 318, (ESI^+) 235; HRMS (Cl^+) predicted for $C_{12}H_8O^{79}Br^{35}Cl^{35}Cl$ 316.9136, found 316.9133.

4.5.5. Ethyl (Z)-2-bromo-3-(2-bromo-6-chlorophenyl)acrylate (Table 3, entry 6 substrate). Potassium *tert*-butoxide (336 mg, 3.0 mmol) was added to a solution of ethyl bromo(diethoxyphosphoryl)acetate (906 mg, 3.0 mmol) in THF (10 mL) at 0 °C and stirred at this temperature for 1 h. 2-Bromo-4-chlorobenzaldehyde (500 mg, 2.85 mmol) was added to the solution, the solution heated to 50 °C for 16 h. Water (50 mL) was added and the aqueous phase extracted with ether (3×30 mL), the combined organic phases washed with brine (3×20 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow oil. Purification by flash chromatography (SiO_2, 2.5 to 5% ether/petrol) gave the *styrene* as a white solid (153 mg, 15%); mp 58–59 °C; ν_{max} (thin film/cm^{-1}) 2982, 2928, 1731, 1430, 1268, 1201, 1152, 779, 758; ^1H NMR (400 MHz, $CDCl_3$) 8.07 (s, 1H), 7.55 (d, *J*=8.0 Hz, 1H), 7.41 (d, *J*=8.0 Hz, 1H), 7.19 (dd, *J*=8.0, 8.0 Hz, 1H), 4.39 (q, *J*=8.0 Hz, 2H), 1.41 (t, *J*=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 161.9, 139.7, 135.2, 133.5, 131.0, 130.4, 128.6, 122.8, 121.5, 63.1, 14.1; MS (FI^+) 367.8, 369.8; HRMS predicted for $C_{11}H_9O_2{}^{79}Br^{79}Br^{35}Cl$ 365.8658, found 365.8658.

4.6. General procedure (E) for the preparation of alkenyl-substituted indoles; exemplified by the preparation of *tert*-butyl 4-chloro-2-(4-methoxyphenyl)-1*H*-indole-1-carboxylate (Table 3, entry 1)

DME (0.44 mL) was added to a flask charged with $Pd_2(dba)_3$ (5.1 mg, 5.6 μmol), ligand **12** (8 mg, 16.7 μmol), Cs_2CO_3 (181 mg, 0.56 mmol), *tert*-butyl carbamate (27 mg, 0.23 mmol), 2-[(*Z*)-2-bromo-2-(4-methoxyphenyl)vinyl]-1,3-dichlorobenzene (80 mg, 0.22 mmol) and the solution heated at 90 °C for 16 h. The crude product was filtered through Celite, the Celite washed with DCM (50 mL), and the crude filtrate was reduced to dryness in vacuo to give a brown gum. Purification via flash chromatography (SiO_2, 10% ether/petrol) gave the *indole* as a yellow oil (56 mg, 71%); ν_{max} (thin film/cm^{-1}) 2979, 1736, 1607, 1506, 1249, 1153; ^1H NMR (400 MHz, $CDCl_3$) 8.10 (dd, *J*=6.6, 2.8 Hz, 1H), 7.37 (d, *J*=8.6 Hz, 2H), 7.27–7.10 (m, 2H), 6.96 (d, *J*=8.6 Hz, 2H), 6.65 (s, 1H), 3.87 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.5, 149.9, 141.0, 137.9, 129.9, 128.0, 126.8, 125.4, 124.5, 122.5, 113.6, 113.3, 107.3, 83.8, 55.3, 27.6; MS (FI^+) 380, 382; HRMS (FI^+) for $C_{20}H_{20}{}^{35}ClNaNO_3$ predicted 380.1029, found 380.1024.

4.6.1. tert-Butyl 5-chloro-2-(4-methoxyphenyl)-1H-indole-1-carboxylate (Table 3, entry 2). Prepared using General procedure E, employing 1-bromo-2-[(*Z*)-2-bromo-2-(4-methoxyphenyl)vinyl]-4-chlorobenzene (78 mg, 0.2 mmol), $Pd_2(dba)_3$ (4.5 mg, 5 μmol), ligand **12** (7.2 mg, 15 μmol), *tert*-butyl carbamate (44 mg, 0.26 mmol), Cs_2CO_3 (163 mg, 0.26 mmol) in DME (0.4 mL) gave a crude black oil. Purification via flash chromatography (SiO_2, 5% Et_2O/petrol) gave the *indole* as a white powder (54 mg, 75%); mp 134–135 °C; ν_{max} (thin film/cm^{-1}) 2953, 2907, 2836, 1726, 1502, 1448, 1245; ^1H NMR (400 MHz, $CDCl_3$) 8.12 (d, *J*=8.6 Hz, 1H), 7.51 (d, *J*=2.0 Hz, 1H), 7.34 (d, *J*=8.6 Hz, 2H), 7.27 (dd, *J*=8.6, 2.0 Hz, 1H), 6.95 (d, *J*=8.6 Hz, 2H), 6.45 (s, 1H), 3.87 (s, 3H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 159.4, 150.0, 141.7, 135.6, 130.4, 129.9, 128.3, 126.8, 124.0, 119.7, 116.2, 113.3, 108.6, 83.7, 55.3, 27.6; MS (FI^+) 380, 382; HRMS (FI^+) predicted for $C_{20}H_{20}{}^{35}ClNaNO_3$ 380.1024, found 380.1024.

4.6.2. tert-Butyl 6-chloro-2-(4-methoxyphenyl)-1H-indole-1-carboxylate (Table 3, entry 3). Prepared using General procedure E, employing 1-bromo-2-[(*Z*)-2-bromo-2-(4-methoxyphenyl)vinyl]-5-chlorobenzene (100 mg, 0.25 mmol), $Pd_2(dba)_3$ (5.7 mg, 6.2 μmol), ligand **12** (118 mg, 18.6 μmol), Cs_2CO_3 (201 mg, 0.62 mmol), *tert*-butyl carbamate (29 mg, 0.25 mmol) in DME (0.5 mL) gave the crude product as a black oil. Purification via flash chromatography (SiO_2, 5% Et_2O/petrol) gave the *indole* as a white solid (72 mg, 81%); mp 122–123 °C; ν_{max} (thin film/cm^{-1}) 2979, 2932, 2836, 1731, 1503, 1323, 1247, 1158; ^1H NMR (400 MHz, $CDCl_3$) 8.26 (d, *J*=2.0 Hz, 1H), 7.44 (d, *J*=8.4 Hz, 1H), 7.35 (d, *J*=8.8 Hz, 2H), 7.23 (dd, *J*=8.4, 2.0 Hz, 1H), 6.96 (d, *J*=8.8 Hz, 2H), 6.48 (s, 1H), 3.87 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.4, 149.9, 141.0, 137.6, 129.9, 127.7, 126.9, 123.4, 120.9, 155.5, 113.3, 109.0, 83.8, 55.3, 27.6 (one quaternary carbon not observed); MS (FI) 380; HRMS (FI) predicted for $C_{20}H_{20}{}^{35}ClNaNO_3$ 380.1025, found 380.1024.

4.6.3. 2-Bromo-1-chloro-3-[(4-methoxyphenyl)ethynyl]benzene (Table 3, entry 4). Prepared using General procedure E, employing 1-bromo-2-[(*Z*)-2-bromo-2-(4-methoxyphenyl)vinyl]-6-chlorobenzene (85 mg, 0.21 mmol), $Pd_2(dba)_3$ (4.8 mg, 5.2 μmol), ligand **12** (7.5 mg, 16 μmol), Cs_2CO_3 (172 mg, 0.53 mmol) and *tert*-butyl carbamate (26 mg, 0.22 mmol) to give the *alkyne* as a yellow solid (58 mg, 78%); mp 53–54 °C; ν_{max} (thin film/cm^{-1}) 2972, 2936, 2839, 2222, 2193, 1603, 1572, 1508, 1399, 1245, 1023, 831; ^1H NMR (400 MHz, $CDCl_3$) 7.53 (d, *J*=8.8 Hz, 2H), 7.44 (dd, *J*=7.8, 1.6 Hz, 1H), 7.22 (dd, *J*=7.8, 7.8 Hz, 1H); 7.39 (dd, *J*=7.8, 1.2 Hz, 1H), 6.91 (d, *J*=8.8 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.1, 135.2, 133.2, 130.9, 129.4, 128.1, 127.7, 125.5, 114.6, 114.1, 94.8, 86.9, 55.3; MS (EI^+) 322; HRMS (EI^+) predicted for $C_{15}H_{10}{}^{79}Br^{35}ClO$ 319.9604, found 319.9604.

4.6.4. tert-Butyl 4-chloro-2-(3-furyl)-1H-indole-1-carboxylate (Table 3, entry 5). Prepared using General procedure E, employing 3-[(*Z*)-1-bromo-2-(2,6-dichlorophenyl)vinyl]furan (100 mg, 0.31 mmol), $Pd_2(dba)_3$ (7.2 mg, 8 μmol, 2.5 mol %), ligand **12** (11.2 mg, 24 μmol), Cs_2CO_3 (252 mg, 0.78 mmol) and *tert*-butyl carbamate (41 mg, 0.35 mmol) in toluene (0.62 mL) to give the *indole* as a yellow oil after purification via flash chromatography (SiO_2, Et_2O/petrol), (61 mg, 61%); ν_{max} (thin film/cm^{-1}); ^1H NMR (400 MHz, $CDCl_3$,) 8.06 (dd, *J*=6.0, 0.8 Hz, 1H), 7.65 (m, 1H), 7.49 (m, 1H), 7.20–7.33 (m, 2H), 6.70 (br s, 1H), 6.56 (m, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.8, 142.3, 140.6, 137.8, 132.9, 127.8, 125.4, 124.7, 122.5, 118.9, 113.9, 112.7, 108.0, 84.4, 27.8; MS (ES^+) 340; HRMS (ES^+) predicted for $C_{17}H_{16}{}^{35}ClNNaO_3$ 340.0712, found 340.0711.

4.6.5. 1-tert-Butyl 2-ethyl 4-chloro-1H-indole-1,2-dicarboxylate (Table 3, entry 6). Prepared using General procedure E, employing ethyl (*Z*)-2-bromo-3-(2-bromo-6-chlorophenyl)acrylate (100 mg, 0.27 mmol), ligand **12** (9.7 mg, 20.4 μmol), Cs_2CO_3 (220 mg, 0.68 mmol), *tert*-butyl carbamate (35 mg, 0.3 mmol) and $Pd_2(dba)_3$ (6.2 mg, 6.8 μmol). Purification by flash chromatography (SiO_2, 5% ether/petrol) gave the *indole* as a yellow oil (53 mg, 61%); ν_{max} (thin film/cm^{-1}) 2982, 1734, 1325, 1278, 1212, 1155; ^1H NMR (400 MHz, $CDCl_3$), 7.99 (d, *J*=8.4 Hz, 1H), 7.33 (dd, *J*=8.4 Hz, 1H), 7.27 (d, *J*=8.4 Hz, 1H), 7.21 (s, 1H), 4.40 (q, *J*=7.2 Hz, 2H), 1.64 (s, 9H), 1.42 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 161.5, 148.9, 138.2, 131.2, 127.8, 127.3, 126.5, 123.0, 113.4, 112.4, 85.1, 61.6, 27.8, 14.3; MS (ES^+) 346; HRMS (ES^+) predicted for $C_{16}H_{18}{}^{35}ClO_4Na$ 346.0811, found 346.0817.

Acknowledgements

This work was supported by the EPSRC and GlaxoSmithKline.

References and notes

1. General indole synthesis reviews; (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875; (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045; (c) Sunberg, R. J. *Indoles*; Academic: London, 1996.
2. (a) *Palladium in Heterocyclic Chemistry*, 2nd ed.; Li, J. J., Gribble, G. W., Eds.; Elsevier: Oxford, 2007; (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285;

(c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644; (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873; (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.
3. (a) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036; (b) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245; (c) Chinchilla, R.; Nájera, C,; Yus, M. *Chem. Rev.* **2004**, *104*, 2667.
4. For reviews, see: (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792; (b) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269; (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447; (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.
5. For recent examples of indole modification by direct C–H functionalization, see: (a) Luzung, M. R.; Lewis, C. A.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7025; (b) Ackermann, L.; Barfuesser, S. *Synlett* **2009**, 808; (c) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159; (d) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926; (e) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172; (f) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoe, B. *Org. Lett.* **2007**, *9*, 3137; (g) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125.
6. For a recent preparation of 2-brominated indoles, see: Newman, S. G.; Aureggi, V.; Bryan, C. S.; Lautens, M. *Chem. Commun.* **2009**, 5236.
7. (a) Willis, M. C.; Brace, G. N.; Findlay, T. J. K.; Holmes, I. P. *Adv. Synth. Catal.* **2006**, *348*, 851; (b) Fletcher, A. J.; Bax, M. N.; Willis, M. C. *Chem. Commun.* **2007**, 4764; (c) Hodgkinson, R. C.; Schulz, J.; Willis, M. C. *Org. Biomol. Chem.* **2009**, *7*, 432.
8. Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403.
9. For application of the same substrate class to benzofuran and quinolone synthesis, see: (a) Tadd, A. C.; Fielding, M. R.; Willis, M. C. *Tetrahedron Lett.* **2007**, *48*, 7578; (b) Tadd, A. C.; Fielding, M. R.; Willis, M. C. *Org. Lett.* **2009**, *11*, 583.
10. (a) Littke, A. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley: Weinheim, 2009; p 25; (b) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555.
11. Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.
12. Spring, D. R.; Krishnan, S.; Blackwell, H. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1354.
13. Clark, R. D.; Muchowski, J. M.; Souchet, M.; Repke, D. B. *Synlett* **1990**, 207.
14. Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4235.
15. Capkova, K.; Yoneda, Y.; Dickerson, T. J.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6463.
16. Asinger, F. *J. Prakt. Chem.* **1934**, *139*, 296.