Preparation of 5-Heteroaryl Substituted 1-(4-Fluorophenyl)-1*H*-indoles via Palladium-Catalyzed Negishi and Stille Cross-Coupling Reactions

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Abstract: Palladium-catalyzed Negishi cross-coupling of 5-1-(4-fluorophenyl)indolylzinc chloride with *N*-methyl-halopyrazoles, bromopyridines and bromopyrimidines in gram scale gave the corresponding cross-coupled products in 38−85% yield.

Key words: indoles, Negishi reaction, Stille reaction, cross-coupling, palladium

The 1-(4-fluorophenyl)indole moiety is present in the antipsychotic drug sertindole[2] and in a number of serotonin 5-HT_{2A}[3] and dopamine D_2[4] receptor antagonists. In a drug discovery program targeting central adrenergic α_1 receptors, we recently required an efficient gram scale synthesis of 5-heteroaryl substituted 1-(4-fluorophenyl)indoles.

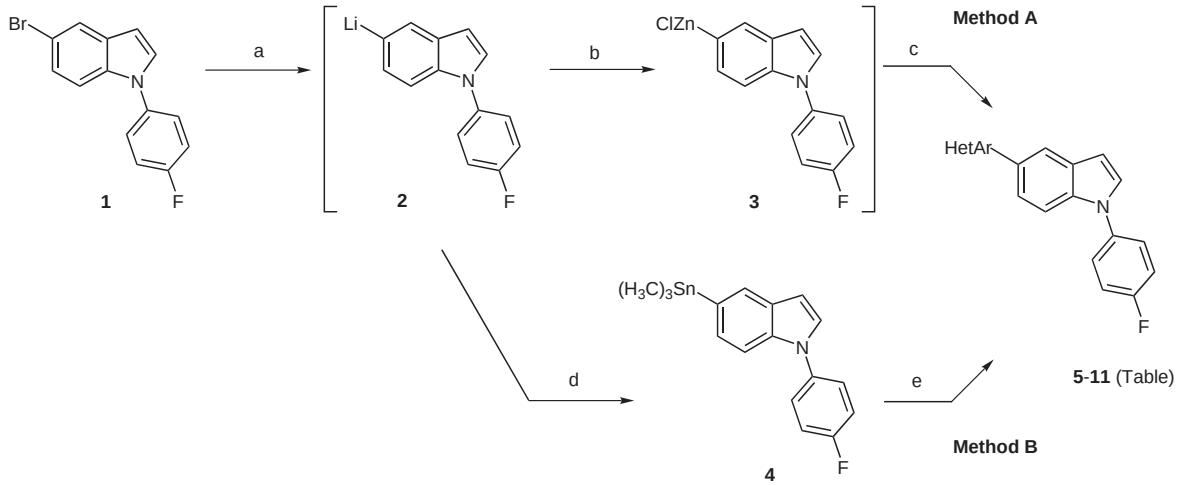
Methods for direct insertion of aromatic substituents in the indole 5-position via palladium-catalyzed cross-coupling of 5-bromo-1*H*-indole with either aryl-boronic acids,[5–7] aryl-stannanes,[8,9] or aryl-zinc halides[10] have been reported. However, only a few examples where the polarity has been reversed have been reported. These involve palladium-catalyzed cross-coupling of 1*H*-indole-5-boronic acid or 5-indolylstannanes with aryl halides.[5,11–15]

Application of the Negishi cross-coupling method offers some advantages over the above mentioned procedures because it can be performed as a one-pot procedure without isolation of the intermediate zinc halides. Furthermore, the by-products are water soluble and non-toxic in contrast to reactions involving tin reagents.

To the best of our knowledge, no Negishi cross-coupling reactions between 5-indolylzinc halide derivatives and aryl halides or heteroaryl halides have been reported to date.

We report herein an efficient one-pot procedure for the synthesis of 5-heteroaryl substituted 1-(4-fluorophenyl)indoles in gram scale,[16] by Negishi cross-coupling reactions. In addition, Stille cross-coupling of 1-(4-fluorophenyl)-5-trimethylstannyl-1*H*-indole (**4**) with selected heteroaryl halides are reported for comparison (Scheme 1).

In order to access the 5-indolylzinc chloride **3** and the 5-indolylstannane **4** required for cross-coupling with relevant heteroaryl halides, we first investigated the bromine-lithium exchange reaction between **1** and *n*-BuLi.



Scheme 1 (a) *n*-BuLi reverse addition, THF, −78 °C, 4 min (b) $ZnCl_2$, THF, −78 °C, 30 min (c) $Pd(PPh_3)_4$, HetAr- X (X = Br, I), DMF 80 °C, 4 h (d) $(CH_3)_3SnCl$ (e) $Pd(PPh_3)_4$, HetAr-X (X = Br, I), DMF, 100 °C, 2 h. See Table for further details.

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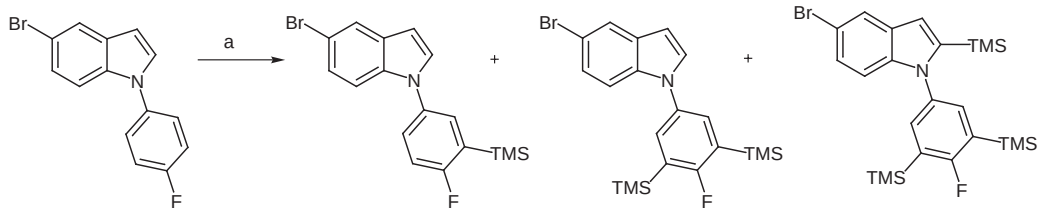


Scheme 2 (a) (*i*) TMS-Cl (4 equiv), THF −78 °C (*ii*) LDA (2.5 equiv), −78 °C, 10 min (*iii*) H_2O (b) Ratio of **12**:**13**:**14** in crude product determined by ^1H NMR: 1:4:1.

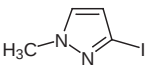
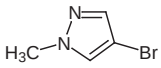
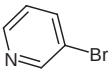
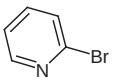
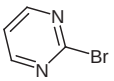
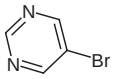
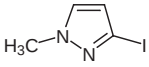
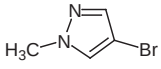
Addition of 1.0 equivalent of *n*-BuLi to a solution of **1** in THF (normal addition) at –78 °C and subsequent quench with MeOH-d_4 after 10 min produced a 1:2:2 mixture of starting material (**1**), the 5-[^{1}H][2] and 5-[^{2}H] debrominated derivatives of **1** as determined by ^1H NMR of the crude product. The 5-bromo derivative **1** isolated from this mixture after chromatography revealed a 10% reduction in the integration of the ^1H NMR signal (δ = 7.13 ppm, CD_2Cl_2) corresponding to the protons in the C-3′ position (ortho to fluorine) in the fluorophenyl group indicating the incorporation of deuterium into this position. This observation together with the relatively high degree of [^{1}H] incorporation in the indole 5-position may be explained by C-3′ deprotonation of unchanged starting material **1** effected by the putative 5-lithio intermediate **2**. The rearrangement of 3- and 5-lithioindoles to the thermodynamically more stable 2-lithioindoles has been reported in the literature.[17] Such rearrangements were avoided by lateral protection of the indole 2-position by the introduction of bulky protecting groups at the indole N-1-position[17,18] or by generation of the indole N-1-anion prior to halogen metal exchange.[19] Apparently the presence of the weak *ortho*-directing fluorine[20,21] in the 4-fluorophenyl substituent at N-1 makes the protons in the C-3′ position more reactive compared to the proton in the indole 2-position. Further support for the generation of a C-3′ lithiated intermediate was obtained by an in situ trapping experiment[22] where a mixture of **1** and trimethylsilyl chloride was treated with 2.5 equivalents of LDA for 10 min at −78 °C. Subsequent quench with water resulted in a 1:4:1 mixture (^1H NMR crude product) of the mono- di- and trisilylated indoles **12**, **13**, and **14** (Scheme 2). Compounds **12** and **13** were isolated and characterised whereas **14** was tentatively assigned based on the ^1H NMR spectrum of the compound containing impurities of **13**.

In contrast to the above described experiments, bromine lithium exchange carried out by addition of a solution of **1** in THF to an excess of *n*-BuLi dissolved in THF (reverse addition) at –78 °C and short reaction times (<4 min) resulted solely in introduction of deuterium in the 5-position of the indole nucleus when quenched with d_4-MeOH.

Thus the 5-indolylzinc chloride **3** used as intermediate in the cross-coupling reactions was generated by reverse addition of up to 73 mmol of **1** to a solution of *n*-BuLi in THF as described above followed by reaction with zinc chloride at –78 °C (Scheme 1). Cross-coupling of **3** with *N*-methyl halopyrazoles as well as bromopyridines and bromopyrimidines in a 2:1 mixture of THF and DMF[23] at 80 °C in the presence of 3 mol% $Pd(PPh_3)_4$ gave a range of 5-heteroaryl substituted 1-(4-fluorophenyl)indoles in 38–85% yield (Table, entries 1−7).

In an alternative protocol (Method B, Scheme 1) **2** (generated as above) was reacted with trimethylstannyl chloride to give the stable and crystalline 5-(trimethylstannyl)-1-(4-fluorophenyl)-1*H*-indole (**4**) in 56% yield (Scheme 1). Cross-coupling between **4** and 3-iodo- or 4-bromo-1-methylpyrazole in DMF in the presence of 2 mol% $Pd(PPh_3)_4$ at 100 °C gave **5** and **6** in 51% and 39% yield respectively (Table entries 8−9). Given the toxicity of tin reagents and the slightly lower yields obtained by Method B compared

Table Preparation of 5-Heteroaryl-1-(4-fluorophenyl)indoles **5**−**11**

Entry	HetAr-X	Method[a]	Product	Yield (%)
1		A	**5**	75
2		A	**6**	38
3		A	**7**	85
4		A	**8**	70
5		A	**9**	80
6		A	**10**	66
7		A	**11**	65
8		B	**5**	51
9		B	**6**	39

[a] See Scheme 1.

to Method A (though only based on two examples), we did not further investigate the use of Method B.

In summary, the present Negishi cross-coupling protocol between the 5-indolyl zinc chloride **3** and heteroaryl halides proved to be an efficient one-pot procedure for gram scale synthesis of 5-heteroaryl substituted 1-(4-fluorophenyl)indoles. The use of reverse addition techniques in the bromine lithium exchange step was crucial to avoid formation of by-products.

All reactions were performed under argon using syringe-septum cap techniques. Glassware was dried in an oven at 150 °C overnight prior to use. THF was freshly distilled from sodium/benzophenone. DMF was sequentially dried and stored over 3 Å molecular sieves. Fresh solns of *n*-BuLi (1.6 M in hexanes) were used throughout. $ZnCl_2$ was flame-dried in vacuo and dissolved to 1.0 M in anhyd THF after cooling to r.t. Silica gel SORBSIL 60 (0.04–0.60 mm) was used for flash chromtography. ^{1}H NMR spectra were recorded for all new compounds at 250 MHz on a Bruker AC 250 or at 500 MHz on a Bruker Avance DRX500 instrument in $CDCl_3$ (99.8%D) or CD_2Cl_2 (99.6%D) with TMS as internal reference. LC-MS data (Liquid Chromatography Mass Spectroscopy) were obtained on a PE Sciex API150EX equipped with a Heated Nebulizer source operating at 425 °C. The LC-MS pumps were Shimadzu 8A series running with a Waters C-18 4.6 × 50 mm, 3.5 μm column. Solvent A: 100% H_2O + 0.05% TFA solvent B: 95% CH_3CN 5% H_2O + 0.035% TFA. Gradient (2 mL/min): 10% B-100% B in 4 min, 10% B for 1 min. Total time including equilibration 5 min. Injection volume 10 μL from a Gilson 215 Liquid Handler.

All reagents were obtained from commercial sources unless otherwise stated: 5-Bromo-1-(4-fluorophenyl)-1*H*-indole was prepared according to published procedures.[2] 3(5)-Iodopyrazole was prepared analogous to the procedure described by Katrizky et al.[24] and subsequently reacted with K_2CO_3/CH_3I in acetone (reflux 8 h), followed by purification using flash chromatography (EtOAc–heptane, 2:98) to give 3-iodo-1-methylpyrazole identical to reference.[25]

Procedure A
Cross-coupling Between 5-Bromo-1-(4-fluorophenyl)-1*H*-indole (1) and Heteroaryl Halides; General Procedure

5-Bromo-1-(4-fluorophenyl)-1*H*-indole (**1**) (5 g, 17.2 mmol) in THF (10 mL) was added during 3 min to a soln of *n*-BuLi (16 mL, 26 mmol) in THF (100 mL) at −78 °C. After stirring for 4 min at −78 °C, a 1 M soln of $ZnCl_2$ (32 mL, 32 mmol) in THF was added and the soln was subsequently stirred for 30 min at −78 °C. The aryl halide (20 mmol), $Pd(PPh_3)_4$ (0.6 g, 0.5 mmol, 3 mol%), and DMF (75 mL) were added. The soln was slowly heated to 80 °C and stirred at this temperature for 4 h. After addition of H_2O (150 mL), the soln was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with H_2O (200 mL) and with a sat. $CaCl_2$ soln (3 × 150 mL) dried over $MgSO_4$ and the solvents were evaporated in vacuo. The crude product was filtered through silica gel (EtOAc–heptane, 75:25) and purified by flash chromatography (EtOAc–heptane–MeOH, 10:90:0→80:0:20). The amounts of reagents and solvents were scaled according to the actual amount of **1** used.

The following compounds were prepared according to Procedure A:

1-(4-Fluorophenyl)-5-(1-methylpyrazol-3-yl)-1*H*-indole (5)
Compound **1** (16.9 mmol) and aryl halide 3-iodo-1-methylpyrazole gave 3.7 g (75%) of the title compound; mp 123–125 °C (toluene).

^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3 H), 6.56 (d, 1 H, *J* = 2.3 Hz), 6.68 (d, 1 H, *J* = 3.3 Hz), 7.10-7.30 (m 3 H), 7.36 (d, 1 H, *J* = 2.4 Hz), 7.40–7.50 (m 3 H), 7.70 (dd 1 H, *J* = 8.5, 1.4 Hz), 8.09 (s, 1 H).

MS: *m*/*z* = 292 (MH^+, 30%).

Anal. Calcd for $C_{18}H_{14}N_3F$: C, 74.21; H, 4.84; N, 14.42. Found: C, 74.50; H, 4.91; N, 14.28.

1-(4-Fluorophenyl)-5-(1-methylpyrazol-4-yl)-1*H*-indole (6)
Compound **1** (24.3 mmol) and aryl halide 4-bromo-1-methylpyrazole gave 2.7 g (38%) of the title compound; mp 144–145 °C (toluene).

^{1}H NMR ($CDCl_3$): δ = 3.94 (s, 3 H), 6.66 (d, 1 H, *J* = 4.0 Hz), 7.10–7.25 (m, 3 H), 7.33 (d, 1 H, *J* = 8.5 Hz), 7.40–7.50 (m, 3 H), 7.60 (d, 1 H *J* = 4.7 Hz), 7.74–7.84 (m, 2 H).

MS: *m*/*z* = 292 (MH^+, 8%).

Anal. Calcd for $C_{18}H_{14}N_3F$: C, 74.21; H, 4.84; N, 14.42. Found: C, 73.93; H, 4.92; N, 13.99.

1-(4-Fluorophenyl)-5-(1-methylpyrazol-5-yl)-1*H*-indole (7)
Compound **1** (11.3 mmol) and aryl halide 5-iodo-1-methylpyrazole gave 2.8 g (85%) of the title compound; mp 135–137 °C (toluene).

^{1}H NMR ($CDCl_3$): δ = 3.91 (s, 3 H), 6.31 (d, 1 H, *J* = 2.4 Hz), 6.73 (d, 1 H, *J* = 3.3 Hz), 7.20–7.30 (m, 3 H), 7.34 (d, 1 H, 3.3 Hz), 7.40–7.60 (m, 4 H), 7.71 (s, 1 H).

MS: *m*/z = 292 (MH^+, 10%).

Anal. Calcd for $C_{18}H_{14}N_3F$: C, 74.21; H, 4.84; N, 14.42. Found: C, 74.32; H, 4.93; N, 14.13.

1-(4-Fluorophenyl)-5-(3-pyridyl)-1*H*-indole (8)
Compound **1** (34.7 mmol) and aryl halide 3-bromopyridine gave 7.0 g (70%) of the title compound; mp 108–110 °C (toluene).

^{1}H NMR ($CDCl_3$): δ = 6.74 (d, 1 H, *J* = 3.3 Hz), 7.17–7.28 (m, 2 H), 7.30–7.40 (m, 2 H), 7.43 (dd, 1 H, *J* = 8.5, 1.4 Hz), 7.45–7.50 (m, 2 H), 7.53 (d, 1 H, *J* = 8.5 Hz), 7.88 (d, 1 H, *J* = 1.1 Hz), 7.92 (dt, 1 H, *J* = 8.0, 1.8 Hz), 8.56 (dd, 1 H, *J* = 4.7, 1.4 Hz), 8.91 (d, 1 H, *J* = 1.8 Hz).

MS: *m*/*z* = 289 (MH^+, 42%).

Anal. Calcd for $C_{19}H_{13}FN_2$: C, 79.15; H, 4.54; N, 9.72. Found: C, 79.07; H, 4.62; N, 9.59.

1-(4-Fluorophenyl)-5-(2-pyridiyl)-1*H*-indole (9)
Compound **1** (34.7 mmol) and aryl halide 2-bromopyridine gave 8.0 g (80%) of the title compound; mp 119–121 °C (toluene).

^{1}H NMR ($CDCl_3$): δ = 6.75 (d, 1 H, *J* = 3.1 Hz), 7.19 (dd, 1 H, *J* = 6.2, 5.9 Hz), 7.21–7.30 (m, 2 H), 7.31 (d, 1 H, *J* = 3.1 Hz), 7.45–7.51 (m, 2 H), 7.53 (d, 1 H, *J* = 8.7 Hz), 7.72 (td, 1 H, *J* = 7.1, 1.4 Hz), 7.79 (d, 1 H, *J* = 7.9 Hz), 7.91 (dd, 1 H, *J* = 8.7, 1.3 Hz), 8.32 (d, 1 H, *J* = 0.8 Hz), 8.70 (d, 1 H, *J* = 4.5 Hz).

MS: *m*/*z* = 289 (MH^+, 59%).

Anal. Calcd for $C_{19}H_{13}FN_2$: C, 79.15; H, 4.54; N, 9.72. Found: C, 79.09; H, 4.62; N, 9.68.

1-(4-Fluorophenyl)-5-(2-pyrimidinyl)-1*H*-indole (10)
Compound **1** (20.4 mmol) and aryl halide 2-bromopyrimidine gave 3.3 g (66%) of the title compound; mp 185–187 °C (toluene).

^{1}H NMR ($CDCl_3$): δ = 6.78 (d, 1 H, *J* = 3.3 Hz), 7.13 (t, 1 H, *J* = 4.7 Hz), 7.20–7.29 (m, 2 H), 7.31 (d, 1 H, *J* = 3.3 Hz), 7.45–7.50 (m, 2 H), 7.52 (d, 1 H, *J* = 8.9 Hz), 8.35 (d, 1 H, *J* = 8.9 Hz), 8.79 (d, 2 H, *J* = 4.7 Hz), 8.83 (s, 1 H).

MS: *m*/*z* = 290 (MH^+, 37%).

Anal. Calcd for $C_{18}H_{12}FN_3$: C, 74.73; H, 4.18; N, 14.52. Found: C, 74.52; H, 3.93; N, 14.31.

1-(4-Fluorophenyl)-5-(5-pyrimidinyl)-1*H*-indole (11)
Compound 1 (72.8 mmol) and aryl halide 5-bromopyridine gave 11.8 g (56%) of the title compound; mp 159–160 °C (toluene).

^{1}H NMR ($CDCl_3$): δ = 6.77 (d, 1 H, *J* = 3.0 Hz), 7.20–7.30 (m, 3 H), 7.42 (dd, 1 H, *J* = 8.5, 1.9 Hz), 7.44–7.49 (m, 3 H), 7.57 (d, 1 H, *J* = 8.5 Hz), 7.89 (d, 1 H, *J* = 1.4 Hz), 9.01 (s, 2 H), 9.18 (s, 1 H).

MS: *m*/*z* = 290 (MH^+, 18%).

Anal. Calcd for $C_{18}H_{12}FN_3$: C, 74.73; H, 4.18; N, 14.52. Found: C, 74.59; H, 4.03; N, 14.35.

1-(4-Fluorophenyl)-5-(trimethylstannyl)-1*H*-indole (4)

5-Bromo-1-(4-fluorophenyl)-1*H*-indole[2] (**1**) (5 g, 17.2 mmol) in THF (20 mL) was added during 3 min to a soln of *n*-BuLi (1.6 M, 26 mmol) in THF (200 mL) at –78 °C. The soln was stirred for 4 min at –78 °C before addition of trimethylstannyl chloride (10 g, 50 mmol) in THF (10 mL). The reaction mixture was allowed to warm up to r.t. and stirred for 1 h. H_2O (75 mL) was added and the aq phase extracted with EtOAc (3 × 75 mL). Evaporation of the solvent and purification by flash chromatography (EtOAc–heptane, 5:100) gave 3.6 g (56%) of **4**; mp 61–63 °C (EtOAc–heptane).

^{1}H NMR ($CDCl_3$): δ = 0.32 (td, 9 H, *J* = 26.8, 0.9 Hz), 6.50 (d, 1 H, *J* = 3.3 Hz), 7.17–7.25 (m, 2 H), 7.24 (d, 1 H, *J* = 3.3 Hz), 7.40–7.44 (m, 2 H), 7.47 (dt, 1 H, *J* = 8.0, 0.9 Hz), 7.82 (td, 1 H, *J* = 24.5, 0.9 Hz).

Anal. Calcd for $C_{17}H_{18}FNSn$: C, 54.59; H, 4.85; N, 3.74. Found: C, 54.98; H, 5.09; N, 3.85.

Procedure B

1-(4-Fluorophenyl)-5-(1-methylpyrazol-3-yl)-1*H*-indole (5)

1-(4-Fluorophenyl)-5-(trimethylstannyl)-1*H*-indole (**4**) (1 g, 2.7 mmol), $Pd(PPh_3)_4$ (62 mg, 0.05 mmol) and 3-iodo-1-methylpyrazole (0.6 g, 2.9 mmol) were dissolved in anhyd DMF (30 mL) and stirred at 100 °C for 2 h. H_2O (50 mL) was added and the soln was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with a sat. soln of $CaCl_2$ (3 × 50 mL), dried ($MgSO_4$) filtered and the solvent was evaporated in vacuo. The compound was purified by preparative TLC (EtOAc–heptane, 1:10) to yield 0.40 g (51%) of **5** identical to the material above.

The following derivative was prepared accordingly:

1-(4-Fluorophenyl)-5-(1-methylpyrazol-4-yl)-1*H*-indole (6)

Aryl halide 4-bromo-1-methylpyrazole when reacted according to procedure B gave the crude product which was purified by flash chromatography (EtOAc–heptane–MeOH, 10:90:0→80:0:20) to yield 0.40 g (39%) of **6** identical to the material above.

5-Bromo-1-(4-fluoro-3-trimethylsilyl-phenyl)-1*H*-indole (12), 5-Bromo-1-(4-fluoro-3,5-bis(trimethylsilyl)-phenyl)-1*H*-indole (13) and 5-bromo-1-(4-fluoro-3,5-bis(trimethylsilyl)-phenyl)-2-trimethylsilyl-1*H*-indole (14)

To a soln of **1** (2 g, 6.9 mmol) in THF (70 mL) at –78 °C was added TMSCl (2.99 g 27.6 mmol) and LDA (17.2 mmol 8.6 mL 2 M soln in THF–heptane–ethylbenzene, 40:20:15). After stirring at –78 °C for 10 min, H_2O (50 mL) was added and the aq phase extracted with EtOAc (2 × 75 mL). Evaporation of the solvent gave 3 g of crude product containing a 1:4:1 mixture of **12**, **13**, and **14** (^{1}H NMR). Flash chromatography (heptane) and evaporation of the fractions containing the fastest eluting compound gave 0.50 g of a 3:7 mixture of **13** and **14**. Compound **14** was tentatively assigned as 5-bromo-1-(4-fluoro-3,5-bis(trimethylsilyl)-phenyl)-2-trimethylsilyl-1*H*-indole (**14**).

R_f 0.88 (EtOAc–heptane, 1:9).

^{1}H NMR (CD_2Cl_2): δ = 0.05 (s, 9 H), 0.29 (s, 18 H), 6.74 (s, 1 H) 6.85 (d, 1 H, *J* = 8.6 Hz), 7.16 (dd, 1 H, *J* = 8.6, 1.9 Hz), 7.31 (d, 2 H, *J* = 4.9 Hz), 7.71 (d, 1 H, *J* = 1.8 Hz).

The next fraction contained 1.0 g (33%) of **13**

R_f 0.83 (EtOAc–heptane, 1:9); mp 104–105 °C (heptane).

^{1}H NMR (CD_2Cl_2): δ = 0.27 (s, 18 H), 6.55 (d, 1 H, *J* = 3.3 Hz), 7.20 (d, 1 H, *J* = 8.0 Hz), 7.23 (d, 1 H, *J* = 8.0 Hz), 7.26 (d, 1 H, *J* = 3.3 Hz), 7.38 (d, 2 H, *J* = 4.7 Hz),7.73 (s, 1 H).

Anal. Calcd for $C_{20}H_{25}BrFNSi_2$: C, 55.29; H, 5.80; N, 3.22. Found: C, 55.22; H, 5.94; N, 3.08.

The last fraction gave 0.10 g (3%) of **12**.

R_f 0.73 (EtOAc–heptane, 1:9); mp 62–63 °C (Et_2O).

^{1}H NMR (CD_2Cl_2): δ = 0.26 (s, 9 H), 6,53 (d, 1 H, *J* = 2.8 Hz), 7.06 (t, 1 H, *J* = 8.0 Hz), 7.19 (dd, 1 H, *J* = 8.7, 1.8 Hz), 7.22 (d, 1 H, *J* = 8.7 Hz), 7.24 (d, 1 H, *J* = 3.0 Hz), 7.32–7.35 (m, 1 H) 7.35–7.39 (m, 1 H) 7.70 (d, 1 H, *J* = 1.4 Hz).

Anal. Calcd for $C_{17}H_{17}BrFNSi$: C, 56.36; H, 4.73; N, 3.87. Found: C, 56.67; H, 4.84; N, 3.81.

In addition, several mixed fractions were obtained.

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