# Synthesis of 4-Substituted 7-Azaindole Derivatives via Pd-Catalyzed C–N and C–O Coupling

Michael Thutewohl,*[1] Hartmut Schirok, Samir Bennabi,[2] Santiago Figueroa-Pérez

Bayer HealthCare AG, Pharma Research, 42096 Wuppertal, Germany
Fax +41(81)7552736; E-mail: mthutewohl@europe.sial.com

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**Abstract:** The efficient substitution of 4-chloro-7-azaindoles by anilines and phenols via palladium-catalyzed C–N and C–O coupling is reported.

**Key words:** 7-azaindoles, palladium catalysis, C–N coupling, C–O coupling, heterocycles

An increasing number of pharmaceutically active compounds with application in various therapeutic areas contain the 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine) pharmacophore,[3] including 4-substituted compounds.[4] The nucleophilic aromatic substitution of 4-chloro-7-azaindole **1**[5] with suitable nucleophiles should provide a convenient access to these derivatives. However, there are only some scattered reports on this kind of reaction, and they appear to be limited to particular reagents like secondary anilines or simple aliphatic alcohols.[6] It was reported that the reaction between **1** and primary anilines **2** does not yield the 4-substituted 7-azaindole **3**. Instead, the rearranged 4-amino-5-azaindole **4** is formed exclusively.[6] The analogous introduction of phenols **5** towards arylethers **6** is not known either.

In this work, we describe the efficient Pd-mediated synthesis of arylaniline- and phenol-substituted compounds of type **3** and **6** (Scheme 1), interesting intermediates in one of our own medicinal chemistry programs based on 7-azaindoles. Recently, the Pd-catalyzed 4-arylation of 7-azaindoles was described,[7] as well as the analogous introduction of allylamine.[8] In our case, we applied a highly active catalyst system containing the bulky and air-stable XPHOS-ligand **7**, offering advantageous properties and versatile applicability for C–N bond formation.[9]

To our delight, attempts to react the electron-poor *p*-nitroanilines **2a**–**c** (Table 1) with 4-chloroazaindoles **1a**–**d** by using *tert*-butanol as solvent and potassium carbonate as base according to literature procedures[9b] proceeded quite well. Other bases like potassium *tert*-butoxide or cesium carbonate, as well as toluene as solvent, gave lower yields. The reaction of **1a**–**d** with 2-fluoro-4-nitroaniline (**2a**) furnished the desired bisarylanilines **3a**–**d** in excellent yields (entries 1–4). In these reactions, the protection of the azaindole N-1 position was not required. With the tosylated (**1c**) or [2-(trimethylsilyl)ethoxy]methyl-protected (SEM-protected) (**1d**) azaindole, the yields were in the same range as with 4-chloroazaindole (**1a**) and 3-methyl-4-chloroazaindole (**1b**). The formation of rearranged products of type **4** was not observed. A comparable result was obtained with 4-nitroaniline (**2b**) (entry 5). In the case of 2-chloro-4-nitroaniline (**2c**), Pd-catalyzed aniline dimerisation occurred reducing the yield (entry 6). The reaction of the electron-rich 4-bisbenzylamino-substituted aniline **2d**[10] also proceeded smoothly (entries 7 and 8). However, in this case the protection of azaindole N1 as tosylate improved the yield significantly (entry 9), because otherwise a yield-reducing N1–C4 azaindole–azaindole self-coupling to products of type **8** took place. To the best of our knowledge, the compounds **3a**–**i** are the first members of this structural class.

The palladium-catalyzed ether formation is still a challenging field, especially because of the disfavored reductive elimination to form the C–O bond due to the Pd–C (LUMO) and Pd–O (HOMO) energy gap.[11] Whilst Hartwig reported ferrocene-based ligands for the generation of diaryl ethers,[12] Buchwald disclosed that electron-rich, sterically bulky monodentate biphenyl dialkylphosphanes are versatile ligands for the Pd-catalyzed C–O bond formation.[13] Recently, Beller described the application of 2-phosphino-*N*-arylpyrrole and -indole ligands (cata*CX*ium®P ligands) for the synthesis of diaryl ethers from aryl chlorides.[14] Even though ligand **7** was only described for Pd(0)-catalyzed C–N coupling, we wanted to study its possible application to a C–O bond formation to introduce phenols into the 4-position of azaindole **1**. In accordance with a general observation reported in the literature, toluene proved to be by far the best solvent for this transformation. In comparison to the conditions described for the anilines, a much longer reaction time was required. Moreover, the outcome of the reaction strongly depended on the electronic character of the appropriate phenol (Table 1). The particularly electron-poor 2-fluoro-4-nitrophenol (**5a**) did not show any reaction (entries 10 and 11). Acetylated or Boc-protected *p*-aminophenols gave the products **6c** and **6d** in moderate yields (entries 12 and 13), while the more-electron-rich nucleophiles **5d**–**f** furnished the desired ethers **6e**–**g** in moderate and good yields, respectively (entries 14–16). This seems to be consistent with literature presenting electron-rich phenols as favored substrates.

In conclusion, we have developed a novel access to 7-azaindole-4-arylanilines and 7-azaindole-4-arylethers via Pd-

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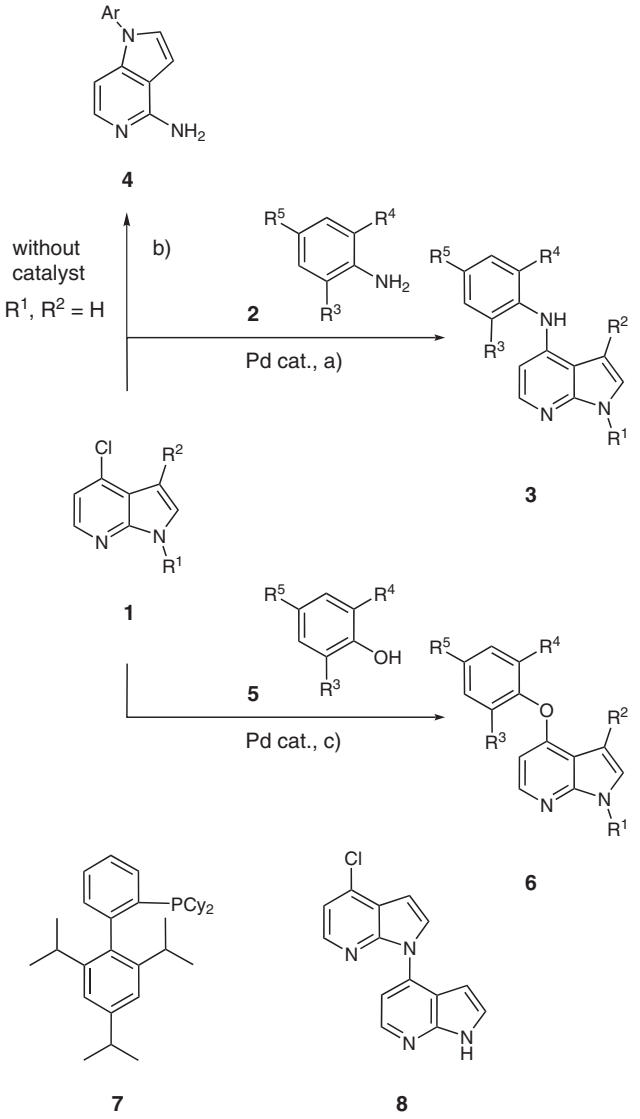


**Scheme 1** Synthesis of 4-arylamino substituted 7-azaindoles. *Reagents and conditions*: a) $Pd_2(dba)_3$ (0.05 equiv), **7** (0.1 equiv), $K_2CO_3$ (2.2 equiv), *t*-BuOH, sealed tube, 100 °C, 3 h; b) Neat, 180 °C, 3 h; c) $Pd_2(dba)_3$ (0.05 equiv), **7** (0.1 equiv), $K_2CO_3$ (2.2 equiv), toluene, sealed tube, 110 °C, overnight.

catalyzed cross-coupling reactions. A number of anilines was introduced in high yields via this method, avoiding a known side reaction. In case of phenols, electron-rich substrates also provided good yields, while electron-poor ones gave only modest yields or did not react at all. Moreover, this is the first example of the application of the XPHOS-ligand for the Pd-catalyzed C–O bond formation.

$^1$H and $^{13}$C NMR spectra were recorded on Bruker Avance spectrometers operating at 300 MHz, 400 MHz ($^1$H), and 125 MHz ($^{13}$C) in DMSO-$d_6$ or $CDCl_3$. Flash column chromatography was performed with silica gel 60 (0.063–0.200 mm) from Merck KGaA, Darmstadt, Germany.

Solvents used as reaction media were purchased in absolute grade and used as received. Commercial reagents were used without purification.

### *N*$^4$,*N*$^4$-Dibenzyl-2,6-difluorobenzene-1,4-diamine (2d)

Ethyl [4-(dibenzylamino)-2,6-difluorophenyl]carbamate was prepared from *N*,*N*-dibenzyl-3,5-difluoroaniline[15] by carboxylation and subsequent Schmidt rearrangement following a procedure disclosed previously.[10]

Ethyl [4-(dibenzylamino)-2,6-difluorophenyl]carbamate (2.10 g, 5.30 mmol) was dissolved in EtOH (40 mL). Powdered KOH (3.0 g, 53 mmol) was added and the mixture was heated to reflux for 20 h. The solvent was evaporated and $H_2O$ (20 mL) and $CH_2Cl_2$ (40 mL) were added. The organic layer was separated and washed with $H_2O$ (3 × 10 mL), then dried over $Na_2SO_4$, and concentrated in vacuo. The residue was dissolved in EtOAc, and charcoal was added. Upon filtration, the solvent was evaporated. After the addition of pentane, the product precipitated and was collected in a suction filter to yield 1.20 g (70%) of the desired aniline as pink crystals.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 4.56 (s, 4 H), 6.21–6.36 (m, 2 H), 7.19–7.36 (m, 10 H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): δ = 54.5, 97.0 (dd, $^2J_{C,F}$ = 17.9 Hz, $^3J_{C,F}$ = 8.7 Hz), 115.0 (t, $^2J_{C,F}$ = 17.7 Hz), 126.6, 126.7, 128.4, 138.8, 139.3 (t, $^3J_{C,F}$ = 11.9 Hz), 152.3 (dd, $^1J_{C,F}$ = 235 Hz, $^3J_{C,F}$ = 11.6 Hz).

HRMS: *m*/*z* [M$^+$] calcd for $C_{20}H_{18}N_2F_2$: 324.1438; found: 324.1431.

### Compounds 3 and 6; General Procedure

A solution of 4-chloroazaindole **1**, nucleophile **2** or **5** (1.2 equiv), tris(dibenzylideneacetone)dipalladium (0.05 equiv), dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (0.1 equiv), and $K_2CO_3$ (2.2 equiv) in degassed *t*-BuOH (for **3**) or degassed toluene (for **6**) (1.5 mL per mmol **1**) was stirred for 3 h at 100 °C (for **3**) or overnight at 110 °C (for **6**) in a sealed pressure tube. After cooling to r.t., the mixture was filtered over celite, washed with EtOAc, and the filtrates were concentrated in vacuo. The residue was purified by flash chromatography (eluents are indicated below) giving the desired products **3** or **6**.

### *N*-(2-Fluoro-4-nitrophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine (3a)

Eluent: cyclohexane–EtOAc (1:1); 78% yield as a yellow solid.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 6.36–6.42 (m, 1 H), 6.81 (d, *J* = 5.4 Hz, 1 H), 7.28–7.37 (m, 2 H), 8.04 (dd, *J* = 8.8, 2.7 Hz, 1 H), 8.10 (d, *J* = 5.2 Hz, 1 H), 8.18 (dd, *J* = 11.5, 2.7 Hz, 1 H), 9.32 (s, 1 H), 11.68 (s, 1 H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): δ = 98.7, 104.9, 111.1, 111.9 (d, $^2J_{C,F}$ = 24.0 Hz), 118.2 (d, $^3J_{C,F}$ = 3.2 Hz), 121.1 (d, $^4J_{C,F}$ = 2.3 Hz), 124.1, 137.6 (d, $^2J_{C,F}$ = 11.6 Hz), 139.6 (d, $^3J_{C,F}$ = 8.1 Hz), 139.9, 143.4, 150.1, 151.1 (d, $^1J_{C,F}$ = 247 Hz).

HRMS: *m*/*z* [M$^+$] calcd for $C_{13}H_9N_4O_2F$: 272.0710; found: 272.0711.

### *N*-(2-Fluoro-4-nitrophenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine (3d)

Eluent: gradient cyclohexane–EtOAc (10:1–8:2); 84% yield as a yellow solid.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = –0.09 (s, 9 H), 0.83 (t, *J* = 8.1 Hz, 2 H), 3.52 (t, *J* = 8.1 Hz, 2 H), 5.60 (s, 2 H), 6.51 (d, *J* = 3.7 Hz, 1 H), 6.85 (d, *J* = 5.1 Hz, 1 H), 7.38 (t, *J* = 8.8 Hz, 1 H), 7.51 (d, *J* = 3.4 Hz, 1 H), 8.05 (dd, *J* = 8.8, 2.6 Hz, 1 H), 8.14 (d, *J* = 5.4 Hz, 1 H), 8.19 (dd, *J* = 11.3, 2.6 Hz, 1 H), 9.39 (s, 1 H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): δ = –1.38, 17.2, 65.3, 72.4, 99.2, 105.3, 111.3, 112.1 (d, $^2J_{C,F}$ = 24.0 Hz), 118.9 (d, $^3J_{C,F}$ = 2.8 Hz), 121.2 (d, $^4J_{C,F}$ = 2.0 Hz), 127.3, 137.3 (d, $^2J_{C,F}$ = 11.3 Hz), 140.4 (d, $^3J_{C,F}$ = 8.3 Hz), 140.7, 143.8, 149.3, 151.5 (d, $^1J_{C,F}$ = 247 Hz).

**Table 1** Synthesis of 4-N- (**3**) and 4-O-Substituted (**6**) 7-Azaindoles[a]

| Entry | SM[b] | $R^1$ | $R^2$ | Nucl. | $R^3$ | $R^4$ | $R^5$ | Prod. | Yield |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | H | H | **2a** | F | H | $NO_2$ | **3a** | 78% |
| 2 | **1b** | H | Me | **2a** | F | H | $NO_2$ | **3b** | 87% |
| 3 | **1c** | Ts | H | **2a** | F | H | $NO_2$ | **3c** | 75% |
| 4 | **1d** | SEM | H | **2a** | F | H | $NO_2$ | **3d** | 84% |
| 5 | **1a** | H | H | **2b** | H | H | $NO_2$ | **3e** | 68% |
| 6 | **1a** | H | H | **2c** | Cl | H | $NO_2$ | **3f** | 26% |
| 7 | **1a** | H | H | **2d** | F | F | $NBn_2$ | **3g** | 42% |
| 8 | **1b** | H | Me | **2d** | F | F | $NBn_2$ | **3h** | 37% |
| 9 | **1e** | Ts | Me | **2d** | F | F | $NBn_2$ | **3i** | 78% |
| 10 | **1a** | H | H | **5a** | F | H | $NO_2$ | **6a** | – |
| 11 | **1c** | Ts | H | **5a** | F | H | $NO_2$ | **6b** | – |
| 12 | **1d** | SEM | H | **5b** | F | H | NHAc | **6c** | 22% |
| 13 | **1d** | SEM | H | **5c** | F | H | NHBoc | **6d** | 37% |
| 14 | **1d** | SEM | H | **5d** | H | H | H | **6e** | 56% |
| 15 | **1d** | SEM | H | **5e** | H | H | Me | **6f** | 64% |
| 16 | **1d** | SEM | H | **5f** | Me | H | H | **6g** | 73% |

[a] Method A for anilines **2**: 0.05 equiv $Pd_2(dba)_3$, 0.1 equiv **7**, 1.2 equiv **2**, 2.2 equiv $K_2CO_3$, *t*-BuOH, sealed tube, 100 °C, 3 h. Method B for phenols **5**: 0.05 equiv $Pd_2(dba)_3$, 0.1 equiv **7**, 1.2 equiv **5**, 2.2 equiv $K_2CO_3$, toluene, sealed tube, 110 °C, overnight.
[b] Starting material.

HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{24}N_4O_3FSi$: 403.1597; found: 403.1599.

***N*-(4-Nitrophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine (3e)**
Purification by filtration; 68% yield as a purple solid.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 6.48–6.58 (m, 1 H), 6.97 (d, *J* = 5.3 Hz, 1 H), 7.28–7.42 (m, 3 H), 8.08 (d, *J* = 5.3 Hz, 1 H), 8.19 (d, *J* = 9.2 Hz, 2 H), 9.55 (s, 1 H), 11.62 (s, 1 H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): δ = 98.3, 103.3, 112.3, 116.4, 123.9, 125.7, 139.5, 140.1, 143.6, 148.9, 150.1.

HRMS: *m*/*z* $[M^+]$ calcd for $C_{13}H_{10}N_4O_2$: 254.0804; found: 254.0808.

**$N^4$,$N^4$-Dibenzyl-2,6-difluoro-$N^1$-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl-benzol-1,4-diamine (3g)**
Eluent: gradient cyclohexane–EtOAc (1:1), EtOAc, MeOH–EtOAc (1:100); 42% yield as a yellow solid.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 4.76 (s, 4 H), 5.82 (d, *J* = 5.5 Hz, 1 H), 6.41–6.50 (m, 1 H), 6.49 (d, *J* = 11.5 Hz, 2 H), 7.07–7.12 (m, 1 H), 7.21–7.43 (m, 10 H), 7.76 (d, *J* = 5.5 Hz, 1 H), 7.91 (s, 1 H), 11.25 (s, 1 H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): δ = 54.1, 95.9 (d, $^2J_{C,F}$ = 28.2 Hz), 97.2, 97.7, 104.4 (t, $^2J_{C,F}$ = 17.8 Hz), 107.4, 121.7, 126.6, 127.0, 128.6, 138.1, 143.8, 146.4, 147.8 (t, $^3J_{C,F}$ = 13.2 Hz), 149.4, 159.9 (dd, $^1J_{C,F}$ = 243 Hz, $^3J_{C,F}$ = 8.6 Hz).

HRMS: *m*/*z* $[M^+]$ calcd for $C_{27}H_{22}N_4F_2$: 440.1813; found: 440.1802.

**$N^4$,$N^4$-Dibenzyl-2,6-difluoro-$N^1$-{3-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}benzol-1,4-diamine (3i)**
Eluent: cyclohexane–EtOAc (5:1); 78% yield as a yellowish solid.

$^1$H NMR (300 MHz, DMSO-$d_6$; rotamers in brackets): δ = 2.30 [2.32] (s, 3 H), 2.36 [2.41] (s, 3 H), 4.77 (s, 4 H), 5.89 (d, *J* = 5.7 Hz, 1 H), 6.47 [6.49] (d, *J* = 5.7 Hz, 2 H), 7.16 [7.20] (s, 1 H), 7.17–7.31 (m, 6 H), 7.32–7.42 (m, 6 H), 7.77 [7.82] (d, *J* = 5.7 Hz, 1 H), 7.91 (d, *J* = 8.31 Hz, 2 H), 8.33 (s, 1 H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): δ = 12.9, 21.0, 54.1, 95.8 (d, $^2J_{C,F}$ = 28.0 Hz), 101.4, 103.4 (t, $^2J_{C,F}$ = 17.8 Hz), 109.4, 114.4, 119.9, 128.6, 128.61, 127.0, 127.4, 128.6, 129.8, 134.9, 138.0, 145.1, 145.7, 148.3, 160.0 (dd, $^1J_{C,F}$ = 244 Hz, $^3J_{C,F}$ = 8.3 Hz).

HRMS: *m*/*z* $[M^+]$ calcd for $C_{35}H_{30}N_4O_2F_2S$: 608.2058; found: 608.2070.

***tert*-Butyl-{3-fluoro-4-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)oxy]phenyl}carbamate (6d)**
Eluent: gradient cyclohexane–EtOAc (10:1–2:1); 37% yield as a colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = –0.07 (s, 9 H), 0.92 (t, *J* = 8.1 Hz, 2 H), 1.53 (s, 9 H), 3.54 (t, *J* = 8.1 Hz, 2 H), 5.66 (s, 2 H), 6.40 (d, *J* = 5.5 Hz, 1 H), 6.47 (d, *J* = 3.4 Hz, 1 H), 6.58 (s, 1 H), 7.03 (d, *J* = 9.0 Hz, 1 H), 7.14 (t, *J* = 9.0 Hz, 1 H), 7.24 (d, *J* = 3.4 Hz, 1 H), 7.52 (d, *J* = 12.5 Hz, 1 H), 8.15 (d, *J* = 5.5 Hz, 1 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = –1.47, 17.7, 28.3, 66.2, 73.1, 81.2, 98.5, 101.8, 107.7 (d, $^2J_{C,F}$ = 23.6 Hz), 110.6, 114.2, 123.6,

126.5, 136.8 (d, $^2J_{C,F}$ = 9.5 Hz), 144.7, 150.6, 152.4, 154.7 (d, $^1J_{C,F}$ = 249 Hz), 158.2.

HRMS: *m/z* [M+H]$^+$ calcd for $C_{24}H_{33}N_3O_4FSi$: 474.2219; found: 474.2218.

**4-Phenoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrolo[2,3-*b*]pyridine (6e)**

Eluent: cyclohexane–EtOAc (10:1); 56% yield as yellowish oil.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 9 H), 0.97 (t, *J* = 8.2 Hz, 2 H), 1.60 (s, 9 H), 3.62 (t, *J* = 8.2 Hz, 2 H), 5.73 (s, 2 H), 6.46 (d, *J* = 3.6 Hz, 1 H), 6.56 (d, *J* = 5.5 Hz, 1 H), 7.21–7.32 (m, 4 H), 7.45–7.50 (m, 2 H), (d, *J* = 12.5 Hz, 1 H), 8.22 (d, *J* = 5.5 Hz, 1 H).

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = –1.47, 17.8, 66.2, 73.1, 98.7, 103.0, 111.4, 120.5, 124.8, 126.4, 129.9, 144.8, 150.8, 155.1, 158.1.

HRMS: *m/z* [M+H]$^+$ calcd for $C_{19}H_{25}N_2O_2Si$: 341.1680; found: 341.1685.

**4-(4-Methylphenoxy)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrolo[2,3-*b*]pyridine (6f)**

Eluent: cyclohexane–EtOAc (10:1); 64% yield as colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$): δ = –0.06 (s, 9 H), 0.97 (t, *J* = 8.3 Hz, 2 H), 2.44 (s, 3 H), 3.61 (t, *J* = 8.3 Hz, 2 H), 5.73 (s, 2 H), 6.47 (d, *J* = 5.5 Hz, 1 H), 6.52 (d, *J* = 5.5 Hz, 1 H), 7.08 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 3.5 Hz, 1 H) overlapping with 7.27 (d, *J* = 8.6 Hz, 2 H), 8.21 (d, *J* = 5.5 Hz, 1 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = –1.7, 17.7, 20.8, 66.1, 73.1, 98.7, 103.0, 111.2, 120.5, 126.2, 130.4, 134.6, 144.8, 150.7, 152.7, 158.5.

HRMS: *m/z* [M+H]$^+$ calcd for $C_{20}H_{27}N_2O_2Si$: 355.1837; found: 355.1835.

**4-(2-Methylphenoxy)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrolo[2,3-*b*]pyridine (6g)**

Eluent: cyclohexane–EtOAc (10:1); 73% yield as yellowish oil.

$^1$H NMR (300 MHz, $CDCl_3$): δ = –0.06 (s, 9 H), 0.91 (t, *J* = 8.1 Hz, 2 H), 2.20 (s, 3 H), 3.62 (t, *J* = 8.1 Hz, 2 H), 5.67 (s, 2 H), 6.31 (d, *J* = 5.5 Hz, 1 H), 6.41 (d, *J* = 5.5 Hz, 1 H), 7.08 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.13–7.29 (m, 4 H), 8.13 (d, *J* = 5.5 Hz, 1 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = –1.48, 16.0, 17.7, 66.1, 73.1, 98.6, 102.2, 110.8, 121.4, 125.4, 126.2, 127.3, 130.7, 131.6, 144.8, 150.7, 152.8, 158.3.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{20}H_{27}N_2O_2Si$: 355.1837; found: 355.1836.

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(1) Current address: Sigma-Aldrich Production GmbH, Industriestraße 25, 9471 Buchs, SG, Switzerland.
(2) Current address: Bayer CropScience SA, Fungicide Research, BP 9163, 69263 Lyon, France.
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