Synthesis of 3,4,5-trisubstituted indoles via iterative directed lithiation of 1-(triisopropylsilyl)gramines

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Abstract- Directed lithiation of 1-(triisopropylsilyl)gramines **1** with *tert*-butyllithium followed by reaction with trimethylsilylmethyl azide produced 4-amino-1-(triisopropylsilyl)gramines **7**. The *N*-*tert*-butoxycarbonyl derivatives **8** were lithiated selectively at C-5 with *tert*-butyllithium and the lithiated species were reacted with a variety of electrophiles to give 5-functionalized compounds, **9** and **10**. A facile method to produce 3,4,5-trisubstituted indoles from readily available gramine derivatives is thereby established.

1. Introduction

Functionalization at the 1-, 2-, and 3-positions of the indole ring can be effected easily by conventional methods.[1] On the other hand, regioselective substitution at the benzenoid portion is rather problematic. Consequently, the development of procedures to achieve this objective has been a challenge for synthetic chemists for many years.[2]

In 1993, we reported a facile method to produce 4-substituted indoles via directed lithiation of 1-(triisopropylsilyl)gramine (**1a**) (Scheme 1).[2g] The selective lithiation at the 4-position is achieved by both the *ortho*-directing effect of the *N,N*-dimethylaminomethyl group and the steric shielding of the proton at C-2 by a bulky *N*-triisopropylsilyl group. The synthetic utility of this reaction has been expanded by development of a procedure for further elaboration at the C-3 side chain via the fluoride-induced elimination-addition reaction of 1-(triisopropylsilyl)gramine methiodides (Scheme 2).[3] The combination of these reactions allows short-step synthesis of a wide range of 3,4-disubstituted indoles **3**, including biologically significant natural products and their analogues, such as clavicipitic acids,[4] pyrroloiminoquinone marine alkaloids,[5] indolactam- and teleocidin-class PKC regulators,[6] 4-fluoroserotonine and -melatonine,[7] and so on.[8] Halonium-induced retro-Mannich reaction, recently reported by Snieckus, allows the ring functionalization at C-3 of the gramines (Scheme 2).[9]

Scheme 1

Scheme 2

Iterative directed lithiation proposed by Snieckus is a potentially valuable method to produce multisubstituted aromatics in short steps.[10, 2l] The process is a series of lithiation-electrophilic substitution in which a newly created directing group promotes the next lithiation. We intended to apply this methodology for the synthesis of 3,4,5-trisubstituted indoles starting from 1-(triisopropylsilyl)gramine (**1a**), because no general synthetic approach to such indoles has been reported. The concept is shown in Scheme 3. The initial C-4 lithiation of **1a** followed by quenching with an appropriate

electrophile produces 4-substituted gramine **5** having a directing group (DG) at C-4, which can promote the next lithiation at C-5 to give a variety of 3,4,5-trisubstituted indoles **6**.

Scheme 3

2. Results and discussion

In the synthetic transformation described above, the choice of the directing group at C-4 may be most important. From a practical point of view, we selected *tert*-butoxycarbonylamino (Boc-NH) group as a director, because 1) good directing ability of Boc-NH has been established in the *ortho*-lithiation of aniline derivatives,[11] 2) 4-amino-1-(triisopropylsilyl)gramine is readily available in high yield via directed lithiation of **1**,[2g, 6] 3) the amino group at C-4 of the indoles could be readily transformed to a variety of functionalities *via* diazonium salt displacement reactions,[12] and finally 4) some biologically significant natural products comprise a 4-aminoindole substructure in their molecular framework.[5, 6]

The synthesis of 4-(*N*-*tert*-butoxycarbonyl)amino-1-(triisopropylsilyl)gramines **8** is shown in Scheme 4. Directed lithiation of **1** under the established conditions (*tert*-butyllithium, diethyl ether, -78 °C, 15 min, then 0 °C, 1.5 h)[2g] followed by reaction with trimethylsilylmethylazide[13] produced 4-aminogramines **7a** and **7b** in 79 and 86% yields, respectively. Treatment of **7** with di-*tert*-butyl dicarbonate in refluxing THF gave the corresponding *N*-*tert*-butoxycarbonyl derivatives **8**.

Scheme 4

Ortho-lithiation of *N*-(*tert*-butoxycarbonyl)aniline was achieved for the first time by Muchowski in 1980.[11a] The compound was lithiated with *tert*-butyllithium in THF at –20 °C. In 1992, Stanetty reexamined this reaction precisely and discovered that utilization of diethyl ether instead of THF as a solvent is essential for good and reproducible results.[11d] Thus, we employed the conditions similar to Stannety's for the lithiation of **8**. After some optimization studies using iodomethane as an electrophile, we found that the selective C-5 lithiation can be effected most satisfactorily by treatment of **8a** in diethyl ether with 3.0 equiv. of *tert*-butyllithium at –78 °C for 15 min and then at 0 °C for 1 h. The lithiated species was reacted with a range of electrophiles at 0 °C for 1 h to give 5-substituted compounds **9a-g** in good isolated yields (Table 1, entries 1-7). Utilization of a slight excess of electrophile (1.5 equiv to the substrate) is enough to trap the lithiated species. This means excess *tert*-butyllithium was decomposed by the reaction with the solvent under the lithiation conditions.[11d] A substrate **8b** having a methoxy group at C-6 was also lithiated at C-5 selectively under similar conditions. However, the lithiated species was found to be somewhat unstable under the lithiation conditions and, after quenching with electrophiles, the C-5 substituted products **10a-g** were isolated in moderate yields (Table, entries 8-14).[14]

Table

3. Conclusion

We have developed a general synthetic route to 3,4,5-trisubstituted indoles from readily

available gramine derivatives via an iterative directed lithiation strategy. In view of the facile substitution at C-3 (side chain or ring) of the gramines and the C-4 functionalization of 4-aminoindoles via diazonium salts, the present procedure may open the way to diverse 3,4,5-trisubstituted indoles, which are not readily available by conventional synthetic methodology.

4. Experimental

4.1. General.

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer System 2000 instrument. NMR spectra were recorded on a JEOL JNM-AL400 instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C) using tetramethylsilane as an internal standard. Column chromatography was conducted on Aluminum oxide 90 standardized (Merck KGaA), or Silica Gel 60N, 63-210 μm (Kanto Chemical Co., Inc.). *tert*-Butyllithium was purchased from Aldrich Chemical Co., Inc. and used after titration with 2,5-dimethoxybenzyl alcohol. Diethyl ether and THF were dried over Na-benzophenone ketyl under Ar and distilled immediately before use. 1-(Triisopropylsilyl)gramine (**1a**),[4a] 6-methoxy-1-(triisopropylsilyl)gramine (**1b**),[5a] and trimethylsilylmethyl azide[13] were prepared according to the reported procedures.

4.2. Procedure for the synthesis of 4-amino-1-(triisopropylsilyl)gramines 7.

Under an argon atmosphere, a pentane solution of *tert*-butyllithium (12 mmol) was

added dropwise to a solution of **1** (10 mmol) in diethyl ether (50 mL) at –78 °C. After being stirred for 15 min, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 1.5 h at the same temperature. The reaction mixture was cooled to –78 °C, and a solution of trimethylsilylmethyl azide (1.94 g, 15 mmol) in diethyl ether (3 mL) was added dropwise. After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and quenched with saturated aqueous NH_4Cl. The products were extracted with diethyl ether and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Aluminum oxide 90 standardized (hexane-ethyl acetate=10:1) to give **7**.

4.2.1. 4-Amino-1-(triisopropylsilyl)gramine (7a). According to the procedure described above, **1a** (3.31 g, 10 mmol) was reacted to give **7a** as pale yellow solid (2.75 g, 79%). Mp 97-97.5 °C (pentane); IR (KBr): 3415, 3283, 3165, 3052, 2942, 2866, 2824, 1619, 1585, 1560, 1491, 1459, 1438, 1375, 1315, 1284, 1245, 1130, 1073, 1035, 1017, 1001, 883, 724, 693, 658, 574, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, *J*= 7.6 Hz, 18H), 1.59-1.71 (m, 3H), 2.25 (s, 6H), 3.54 (s, 2H), 5.43 (br s, 2H), 6.31 (d, *J*= 7.4 Hz, 1H), 6.82 (d, *J*= 8.4 Hz, 1H), 6.87-6.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.80, 18.15, 44.55, 56.57, 104.01, 104.32, 115.89, 119.61, 122.59, 128.11, 142.38, 143.32. *Anal.* Calcd for $C_{20}H_{35}N_3Si$: C, 69.51; H, 10.21; N, 12.16. Found: C, 69.48; H, 10.38; N, 12.04.

4.2.2. 4-Amino-6-methoxy-1-(triisopropylsilyl)gramine (7b). According to the procedure described above, **1b** (7.21 g, 20 mmol) was reacted to give **7b** as pale brown solid (6.47 g, 86%). This compound was somewhat unstable and used for the next reaction without further purification. Mp 78-80 °C; IR (KBr): 3398, 3135, 2946, 2867,

2821, 1616, 1589, 1561, 1464, 1200, 1161, 1128, 1012, 882, 692, 652, 515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, *J*= 7.3 Hz, 18H), 1.57-1.67 (m, 3H), 2.24 (s, 6H), 3.50 (s, 2H), 3.77 (s, 3H), 5.47 (br s, 2H), 6.01 (d, *J*= 2.0 Hz, 1H), 6.36 (d, *J*= 2.0 Hz, 1H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.78, 18.18, 44.52, 55.42, 56.55, 88.53, 93.52, 114.32, 115.88, 126.86, 142.63, 143.79, 157.02. *Anal.* Calcd for $C_{21}H_{37}N_3OSi$: C, 67.15; H, 9.93; N, 11.19. Found: C, 67.27; H, 10.27; N, 11.11.

4.3. Procedure for the synthesis of 4-(*N-tert*-butoxycarbonyl)amino-1-(triisopropylsilyl)gramines 8.

Di-*tert*-butyl dicarbonate (1.40 g, 6.4 mmol) was added as a neat liquid to a solution of **7** (6.1 mmol) in THF (30 mL) at room temperature and the solution was refluxed for 2 h. The reaction mixture was then cooled to room temperature, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=10:1) to give **8**.

4.3.1. 4-(*N-tert*-Butoxycarbonyl)amino-1-(triisopropylsilyl)gramine (8a).

According to the procedure described above, **7a** (2.11 g, 6.1 mmol) was reacted to give **8a** as colorless solid (2.46 g, 91%). Recrystallization from hexane gave colorless prisms. Mp 102.5-103.5 °C; IR (KBr): 3124, 2946, 2869, 2825, 2779, 1715, 1624, 1583, 1557, 1488, 1458, 1419, 1288, 1245, 1158, 1015, 1001, 882, 735, 663, 578, 513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, *J*= 7.5 Hz, 18H), 1.53 (s, 9H), 1.60-1.72 (m, 3H), 2.31 (s, 6H), 3.54 (s, 2H), 6.96 (s, 1H), 7.05-7.11 (m, 2H), 7.69 (br s, 1H), 11.61 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.78, 18.09, 28.55, 43.97, 55.95, 78.44, 108.25, 109.58, 114.83, 121.60, 122.43, 128.91, 133.25, 142.83, 154.04. *Anal.* Calcd for $C_{25}H_{43}N_3O_2Si$: C, 67.37; H, 9.72; N, 9.43. Found: C, 67.02; H, 9.76; N, 9.39.

4.3.2. 4-(*N*-*tert*-Butoxycarbonyl)amino-6-methoxy-1-(triisopropylsilyl)gramine (8b). According to the procedure described above, **7b** (5.63 g, 15 mmol) was reacted to give **8b** as colorless solid (5.70 g, 80%). Recrystallization from hexane gave colorless prisms. Mp 108.5-109.5 °C; IR (KBr): 3112, 2947, 2868, 1712, 1639, 1583, 1466, 1412, 1279, 1200, 1163, 1133, 1016, 884, 839, 683, 655, 593, 586, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, *J*= 7.6 Hz, 18H), 1.53 (s, 9H), 1.60-1.70 (m, 3H), 2.31 (s, 6H), 3.50 (s, 2H), 3.84 (s, 3H), 6.64 (d, *J*= 2.1 Hz, 1H), 6.85 (s, 1H), 7.53 (br s, 1H), 11.78 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.76, 18.12, 28.54, 43.91, 55.88, 55.90, 78.52, 93.83, 97.84, 114.69, 116.11, 127.70, 133.57, 143.23, 153.91, 156.60. *Anal*. Calcd for $C_{26}H_{45}N_3O_3Si$: C, 65.64; H, 9.53; N, 8.83. Found: C, 65.59; H, 9.59; N, 8.84.

4.4. Selective C-5 lithiation-electrophilic substitution of 4-(*N*-*tert*-butoxycarbonyl)amino-1-(triisopropylsilyl)gramines 8. General procedure

Under an argon atmosphere, a pentane solution of *tert*-butyllithium (1.4 mmol) was added dropwise to a solution of **8** (0.45 mmol) in diethyl ether (4.5 mL) at –78 °C. After being stirred for 15 min, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 1 h at the same temperature. A solution of an appropriate electrophile (0.68 mmol) in diethyl ether (3 mL) was added and the solution was stirred for an additional 1 h at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl at the same temperature and allowed to warm to room temperature. The products were extracted with diethyl ether and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The

residue was purified by column chromatography over Silica gel 60N using the following eluents: hexane-ethyl acetate=5:1 for **9a**, hexane-ethyl acetate=3:1 for **9b**, **9c**, and **9d**, hexane-ethyl acetate=5:1~3:1 for **9e**, hexane-ethyl acetate=1:1 for **9f**, hexane-ethyl acetate=1:2 for **9g**, hexane-ethyl acetate=2:1 for **10a**, **10b**, **10c**, **10e**, and **10f**, hexane-ethyl acetate=2:1~1:1 for **10d**, ethyl acetate for **10g**. The results are shown in Table.

4.4.1. 4-(*N*-*tert*-Butoxycarbonyl)amino-5-methyl-1-(triisopropylsilyl)gramine (9a). According to the general procedure, **8a** (201 mg, 0.45 mmol) and iodomethane (42 μL, 0.68 mmol) were reacted to give **9a** as colorless solid (188 mg, 91%). Recrystallization from hexane gave colorless prisms. Mp 128.5-129 °C; IR (KBr): 3096, 2948, 2869, 2827, 1718, 1518, 1492, 1459, 1419, 1364, 1306, 1269, 1244, 1160, 1129, 1045, 1009, 883, 786, 730, 647, 579 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, *J*= 7.6 Hz, 18H), 1.53 (s, 9H), 1.59-1.71 (m, 3H), 2.27 (s, 6H), 2.35 (s, 3H), 3.48 (s, 2H), 6.95 (s, 1H), 6.98 (d, *J*= 8.4 Hz, 1H), 7.17 (d, *J*= 8.4 Hz, 1H), 10.36 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.71, 18.07, 28.53, 44.30, 56.13, 78.57, 110.76, 114.76, 124.31, 125.16, 125.27, 129.23, 129.85, 140.96, 154.18. *Anal*. Calcd for $C_{26}H_{45}N_3O_2Si$: C, 67.92; H, 9.87; N, 9.14. Found: C, 67.73; H, 10.18; N, 9.16.

4.4.2. 4-(*N*-*tert*-Butoxycarbonyl)amino-5-chloro-1-(triisopropylsilyl)gramine (9b). According to the general procedure, **8a** (201 mg, 0.45 mmol) and hexachloroethane (160 mg, 0.68 mmol) were reacted to give **9b** as colorless solid (179 mg, 83%). Recrystallization from diethyl ether-hexane gave colorless prisms. Mp 163-164 °C; IR (KBr): 3090, 2948, 2869, 2828, 1724, 1517, 1478, 1416, 1365, 1268, 1251, 1215, 1162, 1041, 1017, 882, 849, 786, 714, 674, 647, 593, 574 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, *J*= 7.5 Hz, 18H), 1.54 (s, 9H), 1.58-1.71 (m, 3H), 2.27 (s, 6H), 3.48 (br s, 2H),

7.01 (s, 1H), 7.15 (d, *J*= 8.8 Hz, 1H), 7.18 (d, *J*= 8.8 Hz, 1H), 10.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.67, 18.00, 28.45, 44.23, 55.72, 79.19, 111.62, 115.21, 121.45, 123.69, 126.42, 128.52, 130.83, 140.99, 153.77. *Anal*. Calcd for $C_{25}H_{42}ClN_3O_2Si$: C, 62.54; H, 8.82; N, 8.75. Found: C, 62.68; H, 9.09; N, 8.70.

4.4.3. 4-(*N*-*tert*-Butoxycarbonyl)amino-5-bromo-1-(triisopropylsilyl)gramine (9c). According to the general procedure, **8a** (201 mg, 0.45 mmol) and 1,2-dibromo-1,1,2,2-tetrafluoroethane (81 μL, 0.68 mmol) were reacted to give **9c** as colorless solid (191 mg, 81%). Recrystallization from diethyl ether-hexane gave colorless prisms. Mp 168.5-169.5 °C; IR (KBr): 3090, 2948, 2869, 2828, 1724, 1473, 1415, 1365, 1268, 1251, 1215, 1161, 1146, 1040, 1015, 882, 782, 586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, *J*= 7.5 Hz, 18H), 1.55 (s, 9H), 1.60-1.70 (m, 3H), 2.26 (s, 6H), 3.47 (br s, 2H), 6.99 (s, 1H), 7.12 (d, *J*= 8.8 Hz, 1H), 7.31 (d, *J*= 8.8 Hz, 1H), 10.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.66, 17.99, 28.47, 44.25, 55.74, 79.20, 111.25, 112.13, 115.19, 126.47, 126.84, 130.17, 130.70, 141.54, 153.68. *Anal.* Calcd for $C_{25}H_{42}BrN_3O_2Si$: C, 57.24; H, 8.07; N, 8.01. Found: C, 56.91; H, 8.22; N, 7.90.

4.4.4. 4-(*N*-*tert*-Butoxycarbonyl)amino-5-formyl-1-(triisopropylsilyl)gramine (9d). According to the general procedure, **8a** (201 mg, 0.45 mmol) and *N*,*N*-dimethylformamide (52 μL, 0.68 mmol) were reacted to give **9d** as colorless solid (175 mg, 82%). Recrystallization from diethyl ether-hexane gave colorless prisms. Mp 158-159 °C; IR (KBr): 3074, 2948, 2868, 2777, 1723, 1681, 1613, 1575, 1474, 1422, 1314, 1253, 1160, 1045, 1015, 884, 797, 654, 580, 572 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, *J*= 7.6 Hz, 18H), 1.53 (s, 9H), 1.61-1.73 (m, 3H), 2.33 (s, 6H), 3.55 (s, 2H), 7.07 (s, 1H), 7.27 (d, *J*= 8.8 Hz, 1H), 7.73 (d, *J*= 8.8 Hz, 1H), 10.12 (s, 1H),

11.38 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.71, 17.98, 28.37, 44.17, 55.71, 79.94, 110.84, 116.41, 121.59, 121.73, 123.91, 130.66, 136.14, 145.94, 155.77, 190.08. *Anal*. Calcd for $C_{26}H_{43}N_3O_3Si$: C, 65.92; H, 9.15; N, 8.87. Found: C, 65.83; H, 9.19; N, 8.77.

4.4.5.

4-(*N-tert*-Butoxycarbonyl)amino-5-[hydroxy(phenyl)methyl]-1-(triisopropylsilyl)gramine (9e). According to the general procedure, **8a** (201 mg, 0.45 mmol) and benzaldehyde (69 μL, 0.68 mmol) were reacted to give **9e** as colorless solid (201 mg, 81%). Recrystallization from diethyl ether-hexane gave colorless prisms. Mp 167-168 °C; IR (KBr): 3449, 3179, 3086, 2949, 2869, 2819, 2773, 1702, 1617, 1523, 1457, 1422, 1367, 1275, 1254, 1159, 1043, 1018, 882, 795, 709, 584 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, *J*= 7.5 Hz, 9H), 1.09 (d, *J*= 7.5 Hz, 9H), 1.55 (s, 9H), 1.55-1.66 (m, 3H), 2.32 (s, 6H), 3.13 (d, *J*= 12.7 Hz, 1H), 3.89 (d, *J*= 12.7 Hz, 1H), 5.31 (br s, 1H), 6.20 (d, *J*= 2.2 Hz, 1H), 6.82 (d, *J*= 8.8 Hz, 1H), 7.00 (s, 1H), 7.14 (d, *J*= 8.8 Hz, 1H), 7.21 (t, *J*= 7.5 Hz, 1H), 7.31 (t, *J*= 7.5 Hz, 2H), 7.47 (d, *J*= 7.5 Hz, 2H), 10.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.68, 18.03, 18.05, 28.50, 44.39, 56.09, 70.03, 80.00, 112.05, 115.23, 123.85, 124.72, 125.97, 126.34, 127.53, 129.00, 130.30, 131.19, 141.80, 144.30, 157.48. *Anal.* Calcd for $C_{32}H_{49}N_3O_3Si$: C, 69.65; H, 8.95; N, 7.61. Found: C, 69.45; H, 9.09; N, 7.63.

4.4.6.

4-(*N-tert*-Butoxycarbonyl)amino-5-(*N-tert*-butylcarbamoyl)-1-(triisopropylsilyl)gramine (9f). According to the general procedure, **8a** (223 mg, 0.50 mmol) and *tert*-butyl isocyanate (86 μL, 0.75 mmol) were reacted to give **9f** as colorless solid (176 mg, 65%). Recrystallization from dichloromethane-pentane gave colorless powder. Mp

145-147 °C; IR (KBr): 3330, 3087, 2951, 2869, 2824, 2778, 1735, 1703, 1655, 1614, 1534, 1458, 1419, 1364, 1314, 1249, 1165, 1043, 1020, 883, 651, 585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, *J*= 7.6 Hz, 18H), 1.46 (s, 9H), 1.53 (s, 9H), 1.59-1.72 (m, 3H), 2.27 (s, 6H), 3.48 (br s, 2H), 6.86 (br s, 1H), 7.02 (s, 1H), 7.25 (d, *J*= 8.6 Hz, 1H), 7.51 (d, *J*= 8.6 Hz, 1H), 10.65 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.69, 18.01, 28.67, 28.87, 44.35, 50.80, 55.89, 79.48, 111.03, 115.67, 123.86, 124.90, 124.95, 128.49, 130.75, 143.43, 155.56, 168.01. *Anal*. Calcd for $C_{30}H_{52}N_4O_3Si$: C, 66.13; H, 9.62; N, 10.28. Found: C, 65.92; H, 9.38; N, 10.13.

4.4.7.

4-(*N-tert*-Butoxycarbonyl)amino-5-(*N,N*-diethylcarbamoyl)-1-(triisopropylsilyl)gramine (9g). According to the general procedure, **8a** (201 mg, 0.45 mmol) and diethylcarbamoyl chloride (86 μL, 0.68 mmol) were reacted to give **9g** as colorless solid (174 mg, 71%). Recrystallization from diethyl ether-hexane gave colorless powder. Mp 133-134 °C; IR (KBr): 3092, 2948, 2869, 2821, 2775, 1724, 1635, 1546, 1458, 1419, 1364, 1313, 1288, 1252, 1174, 1102, 1043, 1013, 882, 787, 655, 583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, *J*= 7.5 Hz, 18H), 1.18 (t, *J*= 7.1 Hz, 3H), 1.24 (t, *J*= 7.1 Hz, 3H), 1.48 (s, 9H), 1.59-1.71 (m, 3H), 2.26 (s, 6H), 3.14 (br d, *J*= 11.7 Hz, 1H), 3.19-3.36 (m, 2H), 3.57-3.72 (m, 1H), 3.72-3.87 (m, 2H), 6.98 (s, 1H), 6.99 (d, *J*= 8.5 Hz, 1H), 7.14 (d, *J*= 8.5 Hz, 1H), 10.80 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.19, 12.71, 13.59, 18.03, 28.55, 38.09, 43.00, 44.31, 55.86, 78.48, 109.34, 115.76, 121.55, 122.78, 124.78, 129.51, 130.15, 142.72, 154.29, 171.43. *Anal*. Calcd for $C_{30}H_{52}N_4O_3Si$: C, 66.13; H, 9.62; N, 10.28. Found: C, 65.96; H, 9.96; N, 10.28.

4.4.8.

4-(*N-tert*-Butoxycarbonyl)amino-6-methoxy-5-methyl-1-(triisopropylsilyl)gramine

(10a). According to the general procedure, **8b** (476 mg, 1.0 mmol) and iodomethane (93 μL, 1.5 mmol) were reacted to give **10a** as colorless solid (292 mg, 60%). Mp 96-98 °C; IR (KBr): 3134, 2949, 2868, 2820, 2776, 1728, 1626, 1558, 1456, 1427, 1365, 1249, 1216, 1171, 1130, 1115, 1048, 1016, 883, 691, 652, 585 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, *J*= 7.6 Hz, 18H), 1.53 (s, 9H), 1.60-1.70 (m, 3H), 2.18 (s, 3H), 2.26 (s, 6H), 3.45 (br s, 2H), 3.81 (s, 3H), 6.78 (s, 1H), 6.85 (s, 1H), 10.42 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.74, 18.12, 28.52, 44.29, 56.05, 56.10, 78.60, 94.00, 114.86, 115.78, 119.26, 127.96, 129.80, 140.42, 154.28, 155.23. *Anal*. Calcd for $C_{27}H_{47}N_3O_3Si$: C, 66.21; H, 9.67; N, 8.58. Found: C, 66.40; H, 10.07; N, 8.61.

4.4.9.

4-(*N-tert*-Butoxycarbonyl)amino-5-chloro-6-methoxy-1-(triisopropylsilyl)gramine (10b). According to the general procedure, **8b** (476 mg, 1.0 mmol) and hexachloroethane (355 mg, 1.5 mmol) were reacted to give **10b** as colorless solid (299 mg, 59%). Recrystallization from diethyl ether-hexane gave colorless prisms. Mp 150-151 °C; IR (KBr): 3170, 2948, 2868, 2821, 2776, 1732, 1618, 1559, 1522, 1470, 1427, 1365, 1244, 1213, 1163, 1047, 1022, 884, 691, 651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, *J*= 7.6 Hz, 18H), 1.54 (s, 9H), 1.58-1.67 (m, 3H), 2.26 (s, 6H), 3.45 (br s, 2H), 3.87 (s, 3H), 6.89 (s, 1H), 6.91 (s, 1H), 10.56 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.70, 18.05, 28.45, 44.22, 55.70, 56.95, 79.21, 95.56, 113.09, 115.16, 120.30, 129.05, 129.56, 140.35, 152.09, 153.61. *Anal*. Calcd for $C_{26}H_{44}ClN_3O_3Si$: C, 61.21; H, 8.69; N, 8.24. Found: C, 61.25; H, 8.82; N, 8.14.

4.4.10.

4-(*N-tert*-Butoxycarbonyl)amino-5-bromo-6-methoxy-1-(triisopropylsilyl)gramine (10c). According to the general procedure, **8b** (476 mg, 1.0 mmol) and

1,2-dibromo-1,1,2,2-tetrafluoroethane (178 μL, 1.5 mmol) were reacted to give **10c** as colorless solid (311 mg, 56%). Recrystallization from diethyl ether-hexane gave colorless prisms. Mp 158.5-159.5 °C; IR (KBr): 3169, 2948, 2868, 2821, 2776, 1732, 1612, 1559, 1517, 1467, 1425, 1365, 1244, 1212, 1163, 1019, 883, 691, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, J= 7.6 Hz, 18H), 1.54 (s, 9H), 1.58-1.67 (m, 3H), 2.26 (s, 6H), 3.48 (br s, 2H), 3.87 (s, 3H), 6.84 (s, 1H), 6.90 (s, 1H), 10.58 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.69, 18.05, 28.47, 44.24, 55.72, 57.00, 79.19, 95.48, 104.12, 115.09, 120.88, 129.05, 131.16, 141.25, 152.78, 153.53. *Anal*. Calcd for $C_{26}H_{44}BrN_3O_3Si$: C, 56.30; H, 8.00; N, 7.58. Found: C, 56.23; H, 8.08; N, 7.40.

4.4.11.

4-(*N-tert*-Butoxycarbonyl)amino-5-formyl-6-methoxy-1-(triisopropylsilyl)gramine (10d). According to the general procedure, **8b** (476 mg, 1.0 mmol) and *N*,*N*-dimethylformamide (116 μL, 1.5 mmol) were reacted to give **10d** as colorless solid (247 mg, 49%). Mp 103-105 °C; IR (KBr): 3102, 2949, 2868, 2823, 2775, 1727, 1687, 1621, 1556, 1468, 1424, 1366, 1336, 1246, 1167, 1048, 1012, 884, 692, 650, 581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, J= 7.6 Hz, 18H), 1.52 (s, 9H), 1.58-1.67 (m, 3H), 2.30 (s, 6H), 3.48 (br s, 2H), 3.86 (s, 3H), 6.74 (s, 1H), 6.92 (s, 1H), 10.29 (s, 1H), 11.32 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.71, 18.03, 28.43, 44.12, 55.64, 56.38, 79.74, 93.61, 113.40, 116.48, 118.48, 129.25, 134.87, 145.82, 154.59, 157.76, 189.48. *Anal*. Calcd for $C_{27}H_{45}N_3O_4Si$: C, 64.38; H, 9.00; N, 8.34. Found: C, 64.44; H, 9.31; N, 8.33.

4.4.12.

4-(*N-tert*-Butoxycarbonyl)amino-5-[hydroxy(phenyl)methyl]-6-methoxy-1-(triisopropylsilyl)gramine (10e). According to the general procedure, **8b** (476 mg, 1.0 mmol)

and benzaldehyde (152 μL, 1.5 mmol) were reacted to give **10e** as colorless solid (304 mg, 52%). Mp 111-113 °C; IR (KBr): 3386, 2949, 2868, 2821, 2776, 1702, 1622, 1557, 1467, 1426, 1367, 1277, 1253, 1169, 1048, 1016, 883, 694, 652, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, *J*= 7.5 Hz, 18H), 1.49 (s, 9H), 1.55-1.68 (m, 3H), 2.27 (s, 6H), 3.26 (d, *J*= 12.5 Hz, 1H), 3.47 (s, 3H), 3.64 (d, *J*= 12.5 Hz, 1H), 4.99 (br s, 1H), 6.21 (d, *J*= 6.5 Hz, 1H), 6.78 (s, 1H), 6.89 (s, 1H), 7.10-7.16 (m, 1H), 7.20-7.26 (m, 2H), 7.32-7.37 (m, 2H), 10.58 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.71, 18.07, 28.47, 44.27, 55.96, 56.26, 69.22, 79.64, 96.41, 115.38, 119.45, 121.55, 125.06, 125.22, 126.98, 128.70, 130.01, 142.14, 145.46, 155.73, 156.60. *Anal*. Calcd for $C_{33}H_{51}N_3O_4Si$: C, 68.12; H, 8.83; N, 7.22. Found: C, 68.07; H, 9.07; N, 7.15.

4.4.13.

4-(*N*-*tert*-Butoxycarbonyl)amino-5-(*N*-*tert*-butylcarbamoyl)-6-methoxy-1-(triisopropylsilyl)gramine (10f). According to the general procedure, **8b** (476 mg, 1.0 mmol) and *tert*-butyl isocyanate (171 μL, 1.5 mmol) were reacted to give **10f** as colorless solid (235 mg, 41%). Recrystallization from diethyl ether-hexane gave colorless powder. Mp 156-158 °C; IR (KBr): 3360, 3187, 2952, 2868, 2821, 2774, 1715, 1649, 1624, 1543, 1459, 1365, 1310, 1251, 1207, 1161, 1049, 1027, 1015, 882, 689, 654, 571, 524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, *J*= 7.5 Hz, 18H), 1.46 (s, 9H), 1.52 (s, 9H), 1.55-1.67 (m, 3H), 2.20 (s, 6H), 3.41 (s, 2H), 3.81 (s, 3H), 6.81 (s, 1H), 6.84 (br s, 1H), 6.88 (s, 1H), 10.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.69, 18.05, 28.66, 28.70, 44.40, 51.05, 56.66, 79.30, 95.39, 115.59, 119.84, 119.86, 128.34, 129.03, 137.80, 142.45, 153.85, 156.38, 166.21. *Anal*. Calcd for $C_{31}H_{54}N_4O_4Si$: C, 64.77; H, 9.47; N, 9.75. Found: C, 64.73; H, 9.57; N, 9.92.

4.4.14.

4-(*N*-*tert*-Butoxycarbonyl)amino-5-(*N*,*N*-diethylcarbamoyl)-6-methoxy-1-(triisopropylsilyl)gramine (10g). According to the general procedure, **8b** (476 mg, 1.0 mmol) and diethylcarbamoyl chloride (190 μL, 1.5 mmol) were reacted to give **10g** as colorless solid (213 mg, 37%). Recrystallization from hexane gave colorless powder. Mp 184-186 °C; IR (KBr): 3134, 2948, 2868, 2819, 2775, 1727, 1623, 1557, 1457, 1427, 1289, 1250, 1212, 1170, 1142, 1046, 1014, 883, 787, 692, 651, 610, 524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, *J*= 7.5 Hz, 9H), 1.13 (d, *J*= 7.5 Hz, 9H), 1.17 (t, *J*= 7.3 Hz, 3H), 1.22 (t, *J*= 7.1 Hz, 3H), 1.47 (s, 9H), 1.57-1.68 (m, 3H), 2.21 (s, 6H), 3.02 (d, *J*= 12.5 Hz, 1H), 3.23-3.39 (m, 2H), 3.49-3.59 (m, 1H), 3.75 (s, 3H), 3.80 (d, *J*= 12.5 Hz, 1H), 3.81-3.90 (m, 1H), 6.71 (s, 1H), 6.86 (s, 1H), 10.28 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.55, 12.72, 12.97, 18.06, 18.09, 28.53, 37.53, 43.00, 44.42, 55.58, 55.80, 78.54, 93.09, 115.76, 116.66, 119.76, 128.65, 129.52, 142.51, 152.84, 154.60, 167.34. *Anal*. Calcd for $C_{31}H_{54}N_4O_4Si$: C, 64.77; H, 9.47; N, 9.75. Found: C, 64.63; H, 9.74; N, 9.80.

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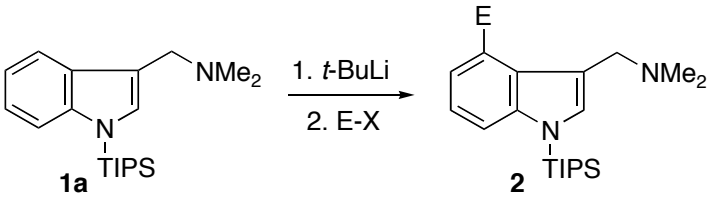
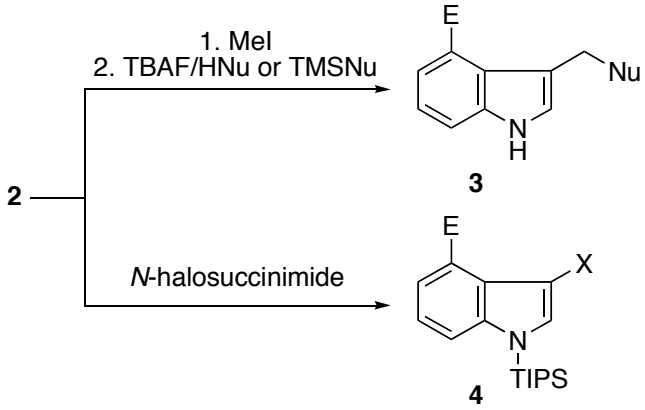
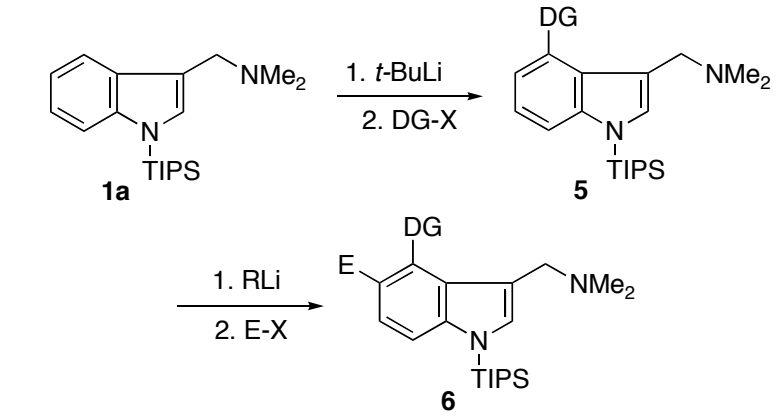
14. It has been reported that *N-tert*-butoxycarbonyl-3-methoxyaniline is not lithiated cleanly or efficiently: see, ref. 11b, c.



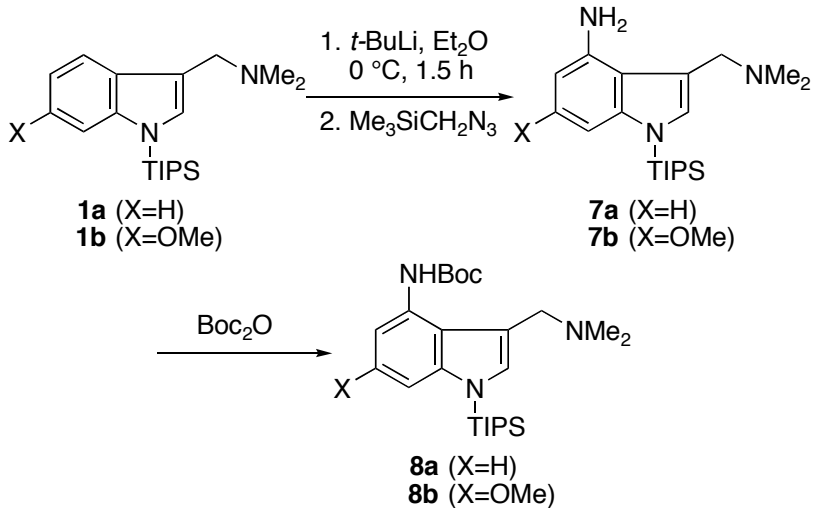
Scheme 1. Directed lithiation of 1-(triisopropylsilyl)gramine (**1a**)



Scheme 2. Functionalization at C-3 (side chain or ring) of gramines **2**

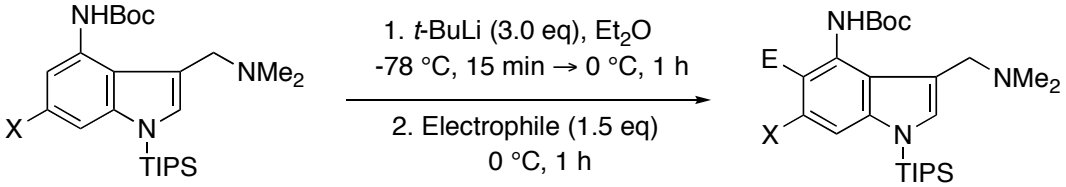


Scheme 3. Iterative directed lithiation of **1a** to produce 3,4,5-trisubstituted indoles **6**



Scheme 4. Synthesis of 4-(*N*-*tert*-butoxycarbonyl)amino-1-(triisopropylsilyl)gramines **8**

Table. Directed lithiation-functionalization at C-5 of 4-(*N*-*tert*-butoxycarbonyl)amino-1-(triisopropylsilyl)gramines **8**



8a (X=H)
8b (X=OMe)

9 (X=H)
10 (X=OMe)

Entry	Substrate	Electrophile	E	Product	Yield (%)[a]
1	**8a**	MeI	Me	**9a**	91
2	**8a**	Cl_3CCCl_3	Cl	**9b**	83
3	**8a**	BrF_2CCBrF_2	Br	**9c**	86
4	**8a**	DMF	CHO	**9d**	82
5	**8a**	PhCHO	CH(OH)Ph	**9e**	81
6	**8a**	*t*-BuNCO	CONH(*t*-Bu)	**9f**	65
7	**8a**	Et_2NCOCl	$CONEt_2$	**9g**	71
8	**8b**	MeI	Me	**10a**	60
9	**8b**	Cl_3CCCl_3	Cl	**10b**	59
10	**8b**	BrF_2CCBrF_2	Br	**10c**	56
11	**8b**	DMF	CHO	**10d**	49
12	**8b**	PhCHO	CH(OH)Ph	**10e**	52
13	**8b**	*t*-BuNCO	CONH(*t*-Bu)	**10f**	41
14	**8b**	Et_2NCOCl	$CONEt_2$	**10g**	37

[a] Isolated yield.

Graphical Abstract

Synthesis of 3,4,5-trisubstituted indoles via iterative directed lithiation of 1-(triisopropylsilyl)gramines

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