Synthesis of 1-[(Tri*Iso*PropylSilyl)Ethynyl]-1,2-BenziodoXol-3(1H)-one (TIPS–EBX) and Alkynylation of Indoles, Thiophenes and Anilines.

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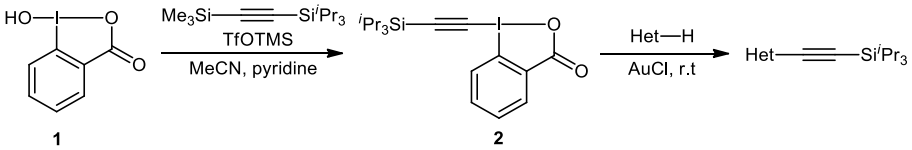
Abstract: An efficient procedure for the 100 mmol (36 g) scale synthesis of 1-[(Tri*Iso*PropylSilyl)Ethynyl]-1,2-BenziodoXol-3(1H)-one (TIPS–EBX, **2**) is reported. The benziodoxolone is then used for the gold-catalyzed direct alkynylation of indole, 2-hexylthiophene and N,N-dibenzylaniline on a 5-10 mmol scale.

Key words: alkynes, arenes, catalysis, heterocycles, iodine.



Scheme 1 Synthesis of 1-[(Tri*Iso*PropylSilyl)Ethynyl]-1,2-BenziodoXol-3(1H)-one **2** and its use in the direct alkynylation of (hetero)aromatics.

The use of hypervalent iodine reagents for C-C bond formation has become increasingly important in addition to their application in oxidation reactions.[1] In this context, Togni's and our group showed the importance of the cyclic benziodoxol(on)e structure for CF_3[2] and alkyne transfer[3] respectively. Indeed, Togni demonstrated that compound **3** and **4** (Figure 1) can be used for CF_3 transfer on malonates, nitroesters and arenes.[2] Our group showed the superiority of compounds **5** and **2** (Figure 1) over classical alkynyliodoniums salts[4] for the ethynylation of β-ketoester, β-nitroesters, β-cyanoester[5] and the oxy- and aminoalkynylation of alkenes.[6]

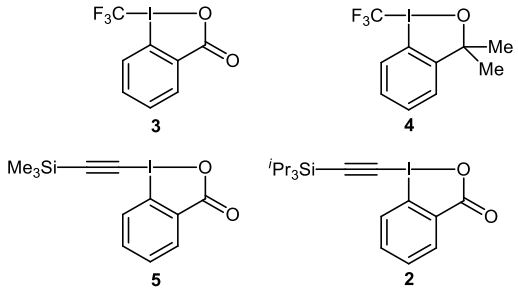
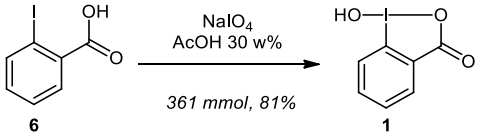


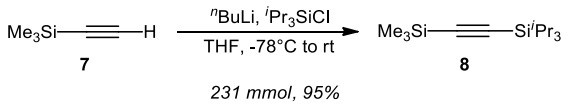
Figure 1 Benziodoxol(on)es used for trifluoromethyl and alkyne transfer.

The discovery of the reactivity of **2** had also an impact in the growing field of direct alkynylation of heterocycles and aromatics.[7,8] The Sonogashira reaction is usually used for the synthesis of alkynyl aromatics.[9] An alternative strategy is based on the use of electrophilic alkynes and unfunctionalized nucleophilic aromatics with the help of metal catalysis. Reagent **2** has shown to have unique properties for the gold-catalyzed alkynylation of indoles, pyrroles, thiophenes and anilines.[7] We report herein a practical procedure for its synthesis and for the direct alkynylation of indole, 2-hexylthiophene and N,N-dibenzylaniline (Scheme 1).

In 1996, Zhdankin reported the first synthesis of TIPS-EBX (**2**) on a 1.5 mmol scale.[10] This reagent did not find application in organic synthesis until our recent work. In order to synthesize larger quantities of TIPS-EBX (**2**), we investigated the scale-up of the originally published procedure. The quality of 2-iodosylbenzoic acid (**1**) was crucial for efficiency and reproducibility. The protocol of Kraszkiewicz and Skulski to access **1** gave best results in this respect (Equation 1).[11] Air drying led to a better quality of reagent when compared to high vacuum drying. The synthesis was scaled up to 0.3 mmol. Taking into account the thermal instability of hypervalent iodine, *this reaction has to be carried out behind a safety shield*. The bis-silylated acetylene **8** was synthesized using a reported procedure (Equation 2).[12]

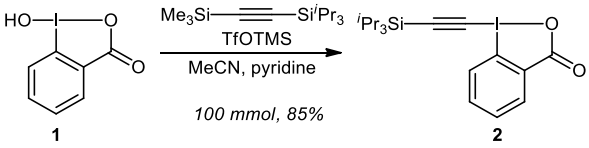


Equation 1 Synthesis of 2-iodosylbenzoic acid (**1**).



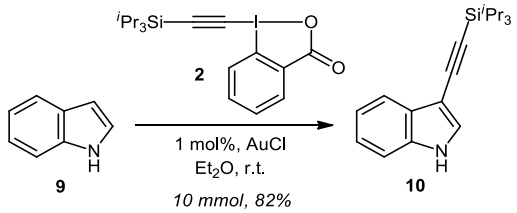
Equation 2 Synthesis of trimethylsilyl(triisopropylsilyl)acetylene (**8**).

The procedure of Zhdankin was then modified for scale up (Equation 3). On larger scale, acidic removal of pyridine and basic removal of 2-iodobenzoic acid (**6**) were essential for an efficient and reproducible purification process. A single recrystallization in CH_3CN generated highly pure crystals, which did not show any sign of decomposition after several months at room temperature under air.[13] The procedure was scaled up to 100 mmol and afforded 36 g of compound **2** (85% yield).



Equation 3 Synthesis of TIPS-EBX (**2**) from 2-iodosylbenzoic acid (**1**).

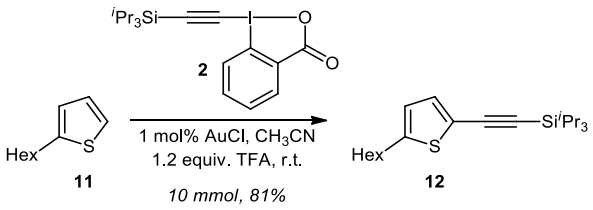
TIPS-EBX (**2**) was then used for the direct alkynylation of indole (**9**) following our previously reported procedure (Equation 4).[8a] The process is highly C_3 regioselective and can be carried out under air and without drying of solvent. On a 10 mmol scale, the use of 1 mol% of AuCl gave 82% yield (2.4 g) after 36 h. 2-Iodobenzoic acid (**6**) can be recovered by acidification of the aqueous layer and extraction with EtOAc in 73% yield. This recycled compound can then be converted into TIPS-EBX (**2**) in two steps.



Equation 4 Gold-catalyzed direct alkynylation of indole (**9**).

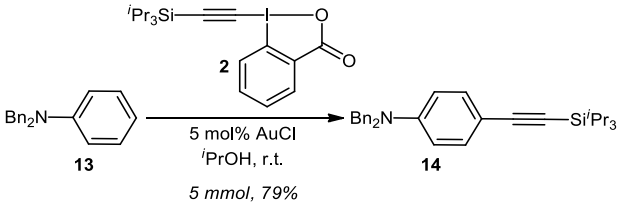
All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. Gold chloride was purchased from Aldrich or Alfa Aesar and kept in desiccator under anhydrous condition (decrease of reactivity has been observed for catalyst after prolonged exposition to air (*ca* 1 month). All chemicals were purchased and used as such unless stated otherwise. Solvents were removed under reduced pressure at 40 °C on a Büchi rotavapor. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d or DMSO-d_6, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm as standard..^{13}C-NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, DMSO-d_6, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-}

The C_2 selective direct alkynylation of 2-hexylthiophene (**11**) was scaled up to a 10 mmol scale using 1 mol% of AuCl and 1.2 equivalent of TFA to give **12** in 81% isolated yield (2.8 g, Equation 5).[8c] 97% of 2-iodobenzoic acid (**6**) was recovered. The generated building block **12** is useful for applications in organic materials.



Equation 5 Gold-catalyzed direct alkynylation of 2-hexylthiophene (**11**).

Finally, N,N-dibenzylaniline (**13**) was successfully *para*-alkynylated in 79% yield at room temperature (Equation 6).[8d] 13% of starting material **13** and 72% of 2-iodobenzoic acid (**6**) could be recovered.



Equation 6 Gold catalyzed direct alkynylation of N,N-dibenzylaniline (**13**).

In conclusion, we have reported an improved synthesis of TIPS-EBX (**2**) on a 100 mmol scale. Both indole (**9**) and 2-hexylthiophene (**11**) were then successfully alkynylated using 1 mol% of AuCl under mild conditions on a 10 mmol scale. Finally, N,N-dibenzylaniline (**13**) was alkynylated using 5 mol% of AuCl on a 5 mmol scale. Further investigation on synthetic applications of TIPS-EBX (**2**) are currently undergoing in our laboratory.

[1] (w = weak, m = medium, s = strong, br = broad). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API.

1-Hydroxy-1,2-benziodoxol-3(*1H*)-one (1)

Caution: reaction carried out behind a safety shield! Following a reported procedure,[11] $NaIO_4$ (77.2 g, 0.361 mol, 1.0 equiv) and 2-iodobenzoic acid (**6**) (89.5 g, 0.361 mmol, 1.0 equiv) were suspended in 30% (v:v) aq. AcOH (700 mL) under air in a 4-neck sulfonation flask equipped with a mechanic stirrer, a thermometer and a condenser. The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (500 mL) and allowed to cool to room temperature, protecting it from light. After 45 min, the suspension was added to water (1.5 L) and the crude product was collected by filtration, washed on the filter with ice water (3 x 300 mL) and cold acetone (3 x 300 mL), and air-dried in the dark overnight to give the pure product **1** (77.3 g, 0.292 mol, 81% yield) as a colorless solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1 H, Ar*H*), 7.97 (m, 1 H, Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1 H, Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1 H, Ar*H*).

^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4.

IR ν 3083 (w), 3060 (w), 2867 (w), 2402 (w), 1601 (m), 1585 (m), 1564 (m), 1440 (m), 1338 (s), 1302 (m), 1148 (m), 1018 (w), 834 (m), 798 (w), 740 (s), 694 (s), 674 (m), 649 (m).[11]

Trimethylsilyl(triisopropylsilyl)acetylene (8)

Following a modified reported procedure,[12] trimethylsilylacetylene (**7**) (30.3 ml, 213 mmol, 1 equiv) was charged in a 4-neck 500 mL flask equipped with a thermometer, a dropping funnel, an agitator magnetic and a nitrogen arrival. THF (330 mL) was added via a dropping funnel and the reaction was cooled to -78°C. ^{n}BuLi (86 mL, 0.21 mmol, 0.98 equiv) was added and the reaction was stirred for 5 minutes at -78°C, then warmed to 0°C and stirred for 5 minutes. The reaction was then cooled back to -78°C and ^{i}Pr$_3$SiCl (45.5 mL, 213 mmol, 1 equiv) was added dropwise via a dropping funnel. The mixture was then allowed to warm to r.t. and stirred overnight. A saturated solution of NH_4Cl (300 mL) was added and the reaction was extracted with Et_2O (2x300 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Distillation of the crude product (1.4 mbar, 55°C) afforded trimethylsilyl (triisopropylsilyl) acetylene (**8**) (51.4 g, 203 mmol, 95%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.08 (m, 21 H, TIPS), 0.18 (s, 9 H, TMS).

IR ν 2959 (m), 2944 (m), 2896 (w), 2867 (m), 1464 (w), 1385 (w), 1250 (m), 996 (w), 842 (s), 764 (s), 675 (m), 660 (m).[12]

1-[(Tri*iso*propyllsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (2)

Caution: reaction carried out behind a safety shield![13] Following a modified reported procedure,[10] 2-iodosylbenzoic acid (**1**) (26.4 g, 100 mmol, 1.0 equiv) was charged in a four-neck flat-bottom flask equipped with a thermometer, a dropping funnel, a mechanic stirrer and a nitrogen arrival. The system was flushed with N_2 by three vacuum/N_2 cycles. Anhydrous acetonitrile (350 mL) was then canulated. The reaction mixture (white suspension) was cooled to 4°C and then trimethylsilyltriflate (20.0 mL, 110 mol, 1.1 equiv) was added dropwise for 15 min via a dropping funnel. The dropping funnel was rinsed with anhydrous acetonitrile (10 mL). No increase of temperature was observed. The ice bath was removed and the reaction stirred for 15 min. Trimethylsilyl)(tri*iso*propylsilyl)acetylene (**8**) (28.0 g, 110 mmol, 1.1 equiv) was added dropwise via dropping funnel over 15 min (the colorless suspension was converted to a yellow solution). The dropping funnel was rinsed with anhydrous acetonitrile (10 mL) and the reaction was stirred for 30 min. Then pyridine (9.9 mL, 25 mmol, 1.1 equiv) was added dropwise via a dropping funnel over 5 min. After 15 min, the reaction mixture was transferred in a one-neck 1L flask and reduced under reduced pressure until a solid was obtained. The solid was dissolved in CH_2Cl_2 (250 mL) and transferred in a 2L separatory funnel. The organic layer was added and washed with 1 M HCl (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (250 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (2x250 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting solid (44.8 g) was then recristallized in CH_3CN (110 mL). The colorless solid obtained over cooling down was then filtered over Büchner, washed with hexanes (2x40 mL) and dried for 1 h at 40°C at 5 mbar. TIPS-EBX (**2**) (36.2 g, 84.5 mmol, 85%) was obtained as white crystals.

Mp 173-177°C (decomposition).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (m, 1 H, ArH), 8.28 (m, 1 H, ArH), 7.72 (m, 2 H, ArH), 1.13 (m, 21 H, TIPS).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 134.5, 132.3, 131.4, 131.4, 126.1, 115.6, 113.9, 64.7, 18.4, 11.1.[10]

3-((Tri*iso*-propylsilyl)ethynyl)-*1H*-indole (10)

2 (5.14 g, 12.0 mmol, 1.2 equiv) was added to a stirring solution of AuCl (23 mg, 0.10 mmol, 0.01 equiv) and **9** (1.17 g, 10.0 mmol, 1.0 equiv) in Et_2O[14] (200 mL) under air in a 500 mL flask. The reaction was sealed and stirred at room temperature for 36 h. Et_2O (250 mL) was added and the organic layer was washed twice with 0.1 M NaOH (250 mL). The

aqueous layers were combined and extracted with Et_2O (250 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (250 mL), brine (250 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (PET/Et_2O 8/2) afforded **10** (2.43 g, 8.17 mol, 82 %) as brown solid.

R*f* 0.4 (PET/Et_2O 7/3).

Mp 55-58°C.

^{1}H NMR ($CDCl_3$, 400MHz) δ 8.11 (br s, 1 H, NH), 7.79 (m, 1 H, ArH), 7.40 (d, *J* = 2.7 Hz, 1 H, ArH), 7.36 (m, 1 H, ArH), 7.26 (m, 2 H, ArH), 1.22 (m, 21 H, TIPS).

^{13}C NMR ($CDCl_3$, 100MHz) δ 135.1, 128.9, 128.3, 123.1, 120.8, 120.1, 111.4, 100.4, 99.3, 92.19, 18.8, 11.5.

IR ν 3407 (m), 3062 (w), 2942 (s), 2891 (m), 2864 (s), 2152 (s), 1620 (w), 1532 (w), 1457 (s), 1416 (m), 1383 (w), 1341 (w), 1325 (m), 1239 (s), 1128 (m), 1071 (m), 996 (m), 910 (m), 883 (s), 774 (s), 742 (s), 676 (s), 658 (s), 628 (s).

HRMS(ESI) calcd for $C_{19}H_{28}NSi^+$ (M+H) 298.1991, found 298.2001.

2-Iodobenzoic acid (**6**) was recovered by adjusting the pH of the NaOH fraction to 1 with conc. HCl and extracting with EtOAc (2x300 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford 2-iodobenzoic acid (**6**) (2.18 g, 8.79 mmol, 73% recovered) as a colorless solid.

((5-Hexylthiophen-2-yl)ethynyl)tri*iso*propylsilane (9)

To a stirring solution of AuCl (23 mg, 0.10 mmol, 0.01 equiv) in CH_3CN[14] (50 mL) was added 2-hexylthiophene (**11**) (1.80 mL, 10.0 mmol, 1 equiv) under air in a 100 mL flask. After 2 min, TFA (0.891 mL, 12.0 mmol, 1.2 equiv) and **2** (5.14 g, 12.0 mmol, 1.2 equiv) were added. The reaction was sealed and stirred at r.t. for 4 days. Et_2O (250 mL) was added, the organic layer was washed twice with 0.1 M NaOH (300 mL). The aqueous layers were combined and extracted with Et_2O (250 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (250 mL), brine (250 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (pentane) and the remaining starting material was removed by heating the oil at 70°C at 0.5 mbar for 4 h to afford **12** (2.83 g, 8.11 mmol, 81 %) as slightly yellow oil.

R*f* 0.6 (pentane, UV).

^{1}H NMR δ 7.08 (d, *J* = 3.5 Hz, 1 H, ArH), 6.65 (d, *J* = 3.5 Hz, 1 H, ArH), 2.80 (t, *J* = 7.5 Hz, 2 H, CH_2), 1.68 (m, CH_2), 1.44-1.30 (m, 6 H, CH_2), 1.15 (m, 21 H, TIPS), 0.93 (t, *J* = 6.1 Hz, 3 H, CH_3).

^{13}C NMR δ 148.1, 132.4, 123.9, 121.0, 99.8, 94.3, 31.7, 31.6, 30.2, 28.7, 22.6, 18.7, 14.1, 11.4.

IR ν 2958 (s), 2928 (s), 2865 (s), 2143 (s), 1535 (w), 1463 (s), 1382 (w), 1367 (w), 1243 (w), 1167 (m), 1074 (w), 1018 (m), 997 (m), 920 (w), 883 (s), 800 (s), 757 (s), 736 (s), 678 (s), 658 (s), 633 (s).

HRMS(ESI) calcd for $C_{21}H_{37}SSi^+$ (M+H) 349.2385, found 349.2381.

2-Iodobenzoic acid (**6**) was recovered by adjusting the pH of the NaOH fraction to 2 with 1 M HCl and extracting with EtOAc (2x250 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford 2-iodobenzoic acid (**6**) (2.91 g, 11.7 mmol, 97% recovered) as a grey solid.

***N*,*N*-Dibenzyl-4-((tri*iso*propylsilyl)ethynyl)aniline (14)**

AuCl (59 mg, 0.025 mmol, 0.05 equiv) was added to a stirring solution of *N*,*N*-dibenzylaniline (**13**) (1.36 g, 5.00 mmol, 1 equiv) and TIPS-EBX (**2**) (3.00 g, 7.00 mmol, 1.4 equiv) in ^{i}PrOH[14] (100 mL) under air in a 250 mL flask. The reaction was stirred at RT for 24 h. EtOAc (200 mL) was added to the reaction mixture. The organic mixture was then washed with 0.1 M NaOH (200 mL), a saturated solution of $NaHCO_3$ (200 mL) and brine (200 mL), dried over $MgSO_4$ and concentrated in vacuum. The resulting oil was purified by column chromatography (pentane/CH_2Cl_2 95/5 to 9/1) to afford **14** (1.66 g, 3.66 mmol, 73%) as a colorless oil and a mixture of **14** and **13** (314 mg, 42w% product **14** and 58w% *N*,*N*-dibenzylaniline **13**, 6% product and 13% recovered starting material) as a colorless oil. Total yield = 79%. Yield based on recovered starting material = 91%.

R_f (pentane/CH_2Cl_2 9/1) 0.15.

^{1}H NMR (400 MHz, C_6D_6) δ 7.37 (m, 2 H, ArH), 7.18-7.01 (m, 6 H, ArH), 6.95 (m, 4 H, ArH), 6.42 (m, 2 H, ArH), 4.15 (s, 4 H, CH_2), 1.21 (m, 21 H, TIPS).

^{13}C NMR (101 MHz, C_6D_6) δ 149.3, 138.4, 133.9, 128.9, 127.3, 126.9, 112.4, 111.8, 109.6, 87.6, 53.9, 19.1, 11.9.

IR ν 3051 (w), 2943 (w), 2865 (w), 2143 (w), 1606 (m), 1516 (m), 1495 (w), 1454 (w), 1398 (w), 1360 (w), 1266 (m), 1241 (w), 1188 (w), 1075 (w), 997 (w), 955 (w), 884 (w), 841 (w), 818 (w), 737 (s), 698 (m), 677 (m).

HRMS (ESI) calcd for $C_{31}H_{40}NSi^+$ $[M+H]^+$ 454.2925; found 454.2913.

2-Iodobenzoic acid (**6**) was recovered by adjusting the pH of the NaOH fraction to 2 with 1 M HCl and extracting with EtOAc (2x250 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford 2-iodobenzoic acid (**6**) (1.25 g, 5.03 mmol, 72% recovered) as a grey solid.

Acknowledgment

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(13) DSC (Differential Scanning Calorimetry) measurements showed an exothermic degradation of TIPS-EBX (**2**) at 187°C.
(14) Commercial solvent was used without drying or purification procedure.

TIPS–EBX for the Alkynylation of Indoles, Thiophenes and Anilines