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SYNTHESIS OF FURAN-FUSED SILOLE AND PHOSPHOLE BY ONE-POT HALOGEN DANCE/HOMOCOUPLING OF BROMOFURFURAL DERIVATIVE[†]

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[†]This paper is dedicated to Professor Dr. Tohru Fukuyama on celebration of his 70th birthday.

Abstract – Synthesis of a furan-fused silole and phosphole was achieved through a one-pot halogen dance/homocoupling of a bromofurfural derivative followed by the formation of the silole and phosphole skeleton.

Extended π-conjugated aromatic compounds have attracted considerable interest as constituents of functional materials.[1] Among them, furan-fused siloles, germoles, and phospholes have been reported as potential molecules for organic transistor, and a general method for the construction of such a framework is required (Figure 1).[2] Recently we have been engaged in developing synthetic application of furfural (2-formylfuran) as an abundant biomass-derived aromatic compound, which would be a key intermediate as an alternative to the synthesis of aromatic compounds from the fossil fuels. In our previous work, we have synthesized furan-conjugated thiazole, oxazole, and benzoxazole as novel π-extended furan derivatives.[3] In addition, we have developed a method for the introduction of functional groups onto aromatic rings such as thiophenes and furans by a base-promoted halogen dance.[4] Herein we report a one-pot halogen dance/homocoupling of a bromofurfural derivative followed by the one-pot formation of the silole and phosphole.

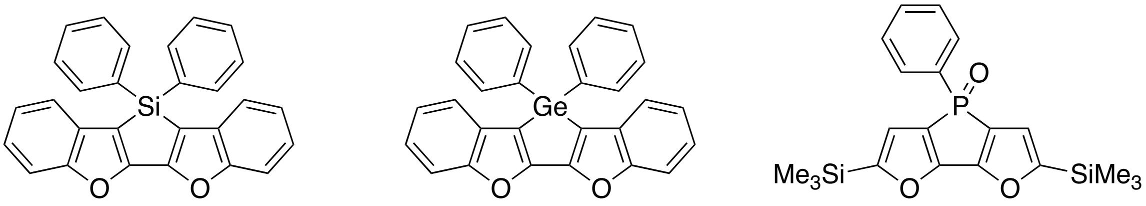
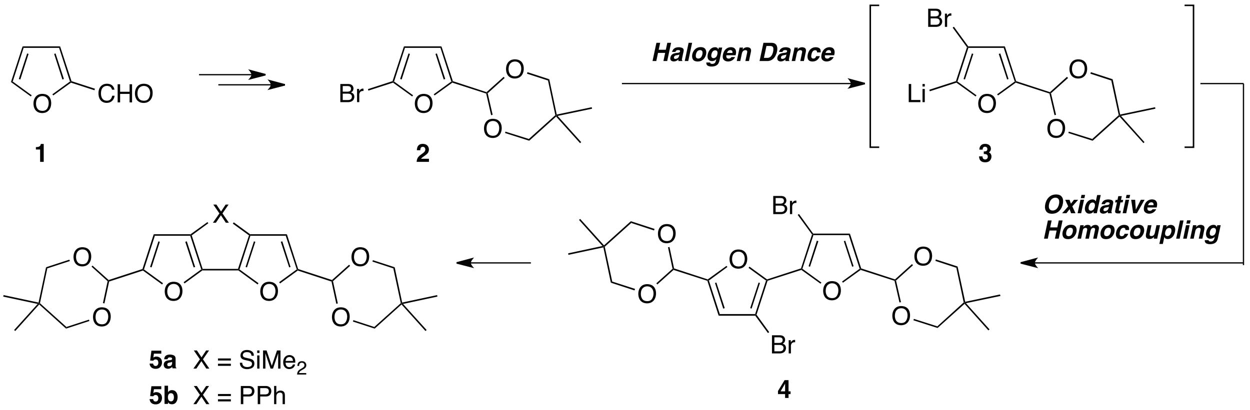


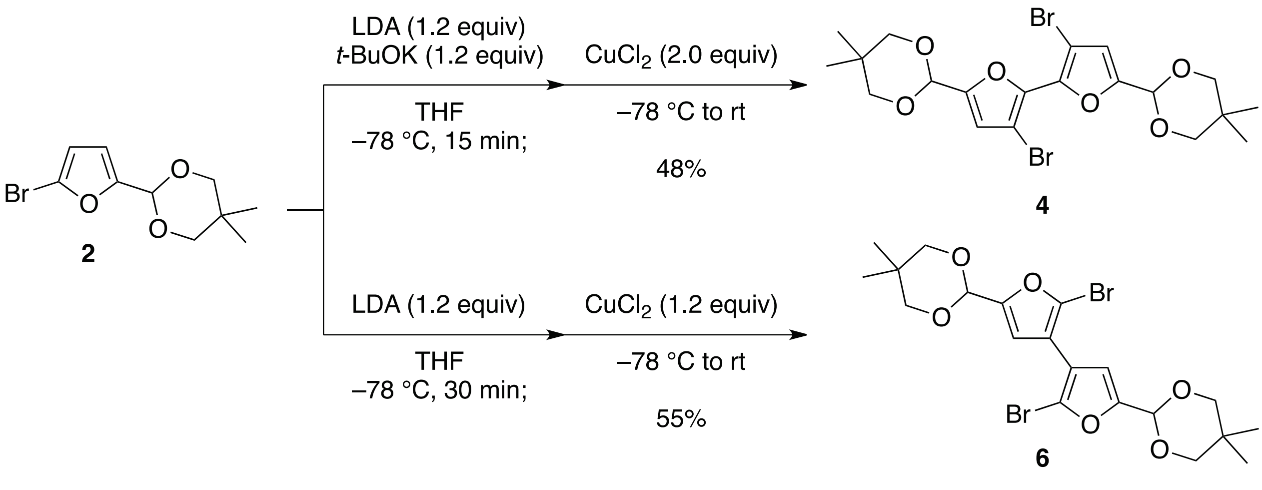
Figure 1. Furan-fused heteroaromatic compounds

Our strategy for the synthesis of a furan-fused silole and phosphole is illustrated in Scheme 1. Furfural (**1**) is converted to 2-bromofuran **2** bearing a cyclic acetal on position 5. For the dimerization, we planned to employ our recent report that 2-bromofuran **2** underwent halogen dance using a combination of LDA and *t*-BuOK.[4e] The resulting furyllithium species **3** were treated with benzaldehyde to provide the corresponding adduct, we then decided to utilize $CuCl_2$ as an oxidant to form its dimer **4**, according to a related transformation.[5] Finally, the formation of silole **5a** and phosphole **5b** would be achieved from the corresponding bromide **4**.



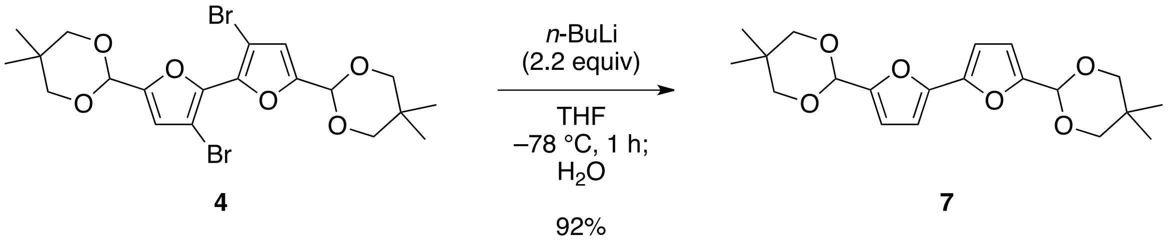
Scheme 1. Our synthetic strategy for a furan-fused silole and phosphole

The synthesis commenced with halogen dance of known 2-bromofuran derivative **2** (Scheme 2). Treatment of compound **2** with LDA and *t*-BuOK at –78 °C for 15 min led to the migration of the bromo group. The resulting furyllithium species were subjected to $CuCl_2$ at room temperature for 17 h to provide the corresponding dimer **4** in 48% yield. We have carried out extensive optimization on the reaction temperature, reaction time, and equivalents of $CuCl_2$; however, the yield was not improved. On the other hand, the same reaction was performed in the absence of *t*-BuOK, which led to the exclusive formation of isomer **6** in 55% yield. The structures were also confirmed by NOE experiments.



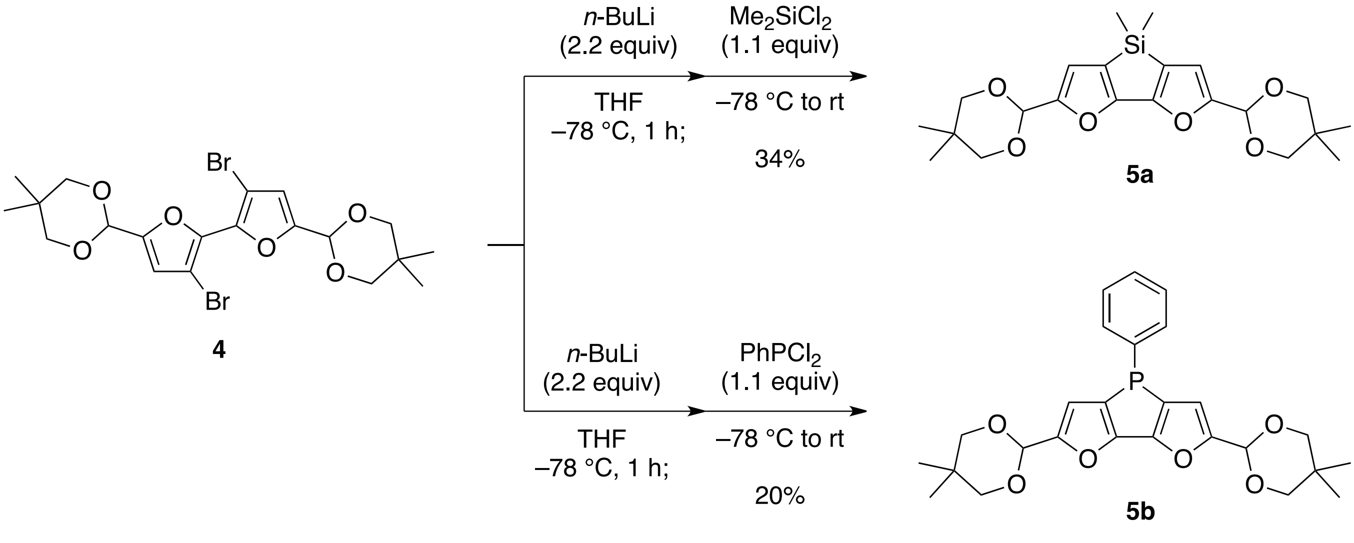
Scheme 2. Oxidative formation of furan dimers

With the furan dimers in hand, we then turned our attention to the construction of the silole and phosphole ring. The reaction conditions for generating anion species by the bromine-lithium exchange were examined for the introduction of the heteroatom (Scheme 3). Treatment of dibromide **4** with 2.2 equivalents of *n*-BuLi at –78 °C for 1 h led to the formation of compound **7** in 92% isolated yield after quenching the resulting reaction mixture with water, which indicated the corresponding dianion species were smoothly generated under the reaction conditions. We also carried out the reaction in a shorter period and found that the starting dibromide **4** was completely consumed to give compound **7** even after 5 min.



Scheme 3. Generation of dianion species with butyllithium

Having established the reaction conditions for the bromine-lithium exchange, we next investigated trapping of the dianion species with an electrophile (Scheme 4). Dibromide **4** was subjected to the conditions, and the resulting reaction mixture was treated with 1.1 equivalents of Me_2SiCl_2 to provide the desired silole **5a** in 34% yield.[6] The corresponding phosphole **5b** was also synthesized in 20% yield with concomitant generation of the phosphine oxide.[7] Addition rate of these electrophiles did not affect the yields of the products. We also attempted to construct the silole and phosphole ring by using furan dimer **6**; however, the desired silole and phosphole were not obtained at all, probably owing to the instability of the corresponding anion species.



Scheme 4. Synthesis of furan-conjugated silole and phosphole

In summary, we have developed a method to synthesize the furan-fused silole and phosphole based on the one-pot halogen dance/oxidative homocoupling of the bromofurfural derivative followed by the one-pot formation of the silole and phosphole ring. This method allows the formation of furan-fused tricyclic skeleton in 4 steps from furfural.

EXPERIMENTAL

General Remarks: Analytical thin layer chromatography (TLC) was performed on Merck 60 F_{254} aluminum sheets precoated with a 0.25 mm thickness of silica gel. Melting points (mp) were measured on a Yanaco MP-J3 and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wave numbers (cm^{-1}). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured on a JEOL ECZ400 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm, tetramethylsilane: δ 0 ppm) and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). High-resolution mass spectra (HRMS) were performed on a JEOL JMS-T100LP AccuTOF LC-Plus (ESI) with a JEOL MS-5414DART attachment. Unless otherwise stated, all reactions were conducted in flame-dried glassware under an inert atmosphere of nitrogen. All work-up and purification procedures were carried out with reagent-grade solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on Wakogel® C-300 (45–75 μm, Wako Pure Chemical Industries, Ltd.). LDA (ca. 1.5 M in THF/ethylbenzene/heptane) was purchased from Tokyo Chemical Industry Co., Ltd (Product number: L0171). Recycling preparative SEC-HPLC was performed with LC-9201 (Japan Analytical Industry Co., Ltd.) equipped with preparative SEC columns (JAI-GEL-1H and JAI-GEL-2H). Anhydrous THF was purchased from Wako Pure Chemical Industries, Ltd.

2-(5-Bromofuran-2-yl)-5,5-dimethyl-1,3-dioxane (2): A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with furfural (**1**) (4.97 mL, 60 mmol, 1.0 equiv), toluene (72 mL), neopentyl glycol (6.25 g, 60 mmol, 1.0 equiv), and *p*-toluenesulfonic acid monohydrate (114.2 mg, 0.60 mmol, 1.0 mol%). The mixture was heated at reflux for 5 h with a Dean-Stark apparatus, at which time the reaction mixture was treated with water. After partitioned, the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/Et_2O = 5:1) to afford the corresponding acetal (9.64 g, 52.9 mmol, 88%) as a colorless oil. A flame-dried 200-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with the acetal (9.64 g, 52.9 mmol, 1.0 equiv) and anhydrous THF (150 mL) under nitrogen atmosphere. NBS (14.1 g, 79.4 mmol, 1.5 equiv) was added to the Schlenk tube at 0 °C and the resulting mixture was stirred at room temperature for 22 h, at which time the reaction mixture was treated with saturated aqueous sodium thiosulfate. After partitioned, the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/Et_2O = 5:1) to afford the title compound (8.67 g, 33.2 mmol, 63%) as a pale yellow solid. R_f = 0.66 (hexane/Et_2O = 2:1); IR (ATR): 1504, 1210, 1104, 1039, 1022, 1014, 986, 978, 914, 809, 781 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.43 (d, J = 3.4 Hz, 1H), 6.29 (d, J = 3.4 Hz, 1H), 5.42 (s, 1H), 3.75 (d, J = 10.2 Hz, 2H), 3.60 (d, J = 10.2 Hz, 2H), 1.26 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 122.3, 112.1, 110.1, 95.6, 77.5, 30.5, 23.0, 21.9; HRMS (DART$^+$) Calcd for $C_{10}H_{14}{}^{79}BrO_3$ $[M+H]^+$: 261.0126; found: *m/z* 261.0118.

3,3'-Dibromo-5,5'-bis(5,5-dimethyl-1,3-dioxan-2-yl)-2,2'-bifuran (4): A flame-dried 200-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with *t*-BuOK (1.35 g, 12 mmol, 1.2 equiv) and anhydrous THF (53.5 mL) under nitrogen atmosphere. The solution was cooled to –78 °C. LDA (1.5 M in THF/ethylbenzene/heptane, 8.0 mL, 12 mmol, 1.2 equiv) was added dropwise to the Schlenk tube and the resulting mixture was stirred at –78 °C for 25 min. To the solution was added 2-bromofuran derivative **2** (2.61 g, 10.0 mmol, 1.0 equiv) in THF (13.0 mL) dropwise and the resulting mixture was stirred at –78 °C for 15 min. The resulting brown solution was treated with $CuCl_2$ (2.69 g, 20.0 mmol, 2.0 equiv) at –78 °C. After stirring at room temperature for 18 h, the reaction mixture was treated with saturated aqueous ammonium chloride. After partitioned, the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/Et_2O = 5:1) to afford the title compound (1.24 g, 2.39 mmol, 48%) as a colorless solid. R_f = 0.76 (hexane/Et_2O = 2:1); IR (ATR): 1152, 1113, 1096, 1016, 981, 967, 923, 815, 625, 553, 533, 513 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.61 (s, 2H), 5.46 (s, 2H), 3.74 (d, J = 11.2 Hz, 4H), 3.60 (d, J = 11.2 Hz, 4H), 1.25 (s, 6H), 0.80 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3, 140.7, 112.9, 101.0, 95.5, 77.5, 30.5, 23.0, 21.9; HRMS (DART$^+$) Calcd for $C_{20}H_{25}{}^{79}Br_2O_6$ $[M+H]^+$: 519.0018; found: *m/z* 519.0014.

2,2'-Dibromo-5,5'-bis(5,5-dimethyl-1,3-dioxan-2-yl)-3,3'-bifuran (6): A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2-bromofuran derivative **2** (783.6 mg, 3.0 mmol, 1.0 equiv) and anhydrous THF (19.8 mL) under nitrogen atmosphere. The solution was cooled to –78 °C. LDA (1.5 M in THF/ethylbenzene/heptane, 2.4 mL, 3.6 mmol, 1.2 equiv) was added dropwise to the Schlenk tube and the resulting mixture was stirred at –78 °C for 30 min. To the solution was added $CuCl_2$ (484.2 mg, 3.6 mmol, 1.2 equiv) at –78 °C. After stirring at room temperature for 28 h, the reaction mixture was treated with saturated aqueous ammonium chloride. After partitioned, the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/Et_2O = 10:1) to afford the title compound (429 mg, 0.83 mmol, 55%) as a beige solid. $R_f = 0.47$ (hexane/Et_2O = 2:1); IR (ATR): 1393, 1153, 1105, 1038, 1023, 986, 967, 909, 812, 643, 630 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.87 (s, 2H), 5.44 (s, 2H), 3.76 (d, *J* = 10.8 Hz, 4H), 3.61 (d, *J* = 10.8 Hz, 4H), 1.27 (s, 6H), 0.80 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5, 120.9, 116.3, 109.7, 95.6, 77.6, 30.5, 23.1, 21.9; HRMS (DART$^+$) Calcd for $C_{20}H_{25}{}^{79}Br_2O_6$ $[M+H]^+$: 519.0018; found: *m/z* 518.9995.

5,5'-Bis(5,5-dimethyl-1,3-dioxan-2-yl)-2,2'-bifuran (7): A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with furan dimer **4** (78.3 mg, 0.15 mmol, 1.0 equiv) and anhydrous THF (1.4 mL) under nitrogen atmosphere. The solution was cooled to –78 °C. To the Schlenk tube was added *n*-BuLi (1.54 M in hexane, 0.22 mL, 0.33 mmol, 2.2 equiv) and the resulting mixture was stirred at –78 °C for 1 h. The reaction mixture was treated with water at –78 °C and warmed to room temperature. After partitioned, the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/Et_2O = 3:2) to afford the title compound (52.6 mg, 0.145 mmol, 97%) as a pale yellow solid. $R_f = 0.44$ (hexane/Et_2O = 3:2); IR (ATR): 1395, 1199, 1103, 1025, 1010, 988, 981, 961, 791, 778, 633 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.56 (d, *J* = 3.4 Hz, 2H), 6.51 (d, *J* = 3.4 Hz, 2H), 5.49 (s, 2H), 3.76 (d, *J* = 10.8 Hz, 4H), 3.62 (d, *J* = 10.8 Hz, 4H), 1.28 (s, 6H), 0.80 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.5, 146.2, 109.2, 106.3, 96.1, 77.5, 30.5, 23.0, 21.9; HRMS (DART$^+$) Calcd for $C_{20}H_{27}O_6$ $[M+H]^+$: 363.1808; found: *m/z* 363.1816.

2,6-Bis(5,5-dimethyl-1,3-dioxan-2-yl)-4,4-dimethyl-4*H*-silolo[3,2-*b*:4,5-*b*']difuran (5a): A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with furan dimer **4** (260.1 mg, 0.50 mmol, 1.0 equiv) and anhydrous THF (5.0 mL) under nitrogen atmosphere. The solution was cooled to –78 °C. To the Schlenk tube was added *n*-BuLi (1.54 M in hexane, 0.72 mL, 1.1 mmol, 2.2 equiv) and the resulting mixture was stirred at –78 °C for 1 h. The reaction mixture was treated with Me_2SiCl_2 (66 μL, 0.55 mmol, 1.1 equiv) at –78 °C. After stirring at room temperature for 7 h, the reaction mixture was treated with saturated aqueous ammonium chloride. After partitioned, the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with water and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/Et_2O = 5:1) to afford the title compound (71.9 mg, 0.17 mmol, 34%) as an orange solid. $R_f = 0.80$ (hexane/Et_2O = 3:2); IR (ATR): 1392, 1133, 1115, 1098, 1038, 988, 971, 958, 855, 841, 780, 690, 668, 653, 643, 633 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.51 (s, 2H), 5.48 (s, 2H), 3.75 (d, *J* = 10.6 Hz, 4H), 3.61 (d, *J* = 10.6 Hz, 4H), 1.28 (s, 6H), 0.79 (s, 6H), 0.35 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3, 152.7, 120.3, 111.7, 96.2, 77.6, 30.5, 23.1, 22.0, –3.7; HRMS (DART$^+$) Calcd for $C_{22}H_{31}O_6Si$ $[M+H]^+$: 419.1890; found: *m/z* 419.1891.

2,6-Bis(5,5-dimethyl-1,3-dioxan-2-yl)-4-phenyl-4*H*-phospholo[3,2-*b*:4,5-*b*']difuran (5b): A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with furan dimer **4** (104.0 mg, 0.20 mmol, 1.0 equiv) and anhydrous THF (2.0 mL) under nitrogen atmosphere. The solution was cooled to –78 °C. To the Schlenk tube was added *n*-BuLi (1.54 M in hexane, 0.29 mL, 0.44 mmol, 2.2 equiv) and the resulting mixture was stirred at –78 °C for 1 h. The reaction mixture was treated with $PhPCl_2$ (29.8 μL, 0.22 mmol, 1.1 equiv) at –78 °C. After stirring at room temperature for 20 h, the reaction mixture was treated with saturated aqueous ammonium chloride. After partitioned, the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/Et_2O = 5:1) to afford the title compound (18.8 mg, 0.040 mmol, 20%) as a beige amorphous. $R_f = 0.44$ (hexane/Et_2O = 3:2); IR (ATR): 1388, 1116, 1099, 1039, 1025, 1015, 989, 809, 799, 744, 691, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.34 (m, 2H), 7.32–7.20 (m, 3H), 6.69 (d, *J* = 2.0 Hz, 2H), 5.51 (s, 2H), 3.75 (d, *J* = 11.2 Hz, 4H), 3.62 (d, *J* = 11.2 Hz, 4H), 1.27 (s, 6H), 0.80 (s, 6H); HRMS (DART$^+$) Calcd for $C_{26}H_{30}O_6P$ $[M+H]^+$: 469.1780; found: *m/z* 469.1798.

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6. Neither the monosilylated furan dimer nor the silicon-tethered oligomer was observed in the reaction, even though the starting furan dimer **4** was completely consumed.
7. During work-up and purification, oxidation of phosphole **5b** to its phosphine oxide was observed.