Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Hydroquinone-Quinone Oxidation by Molecular Oxygen: A Simple Tool for Signal Amplification through Auto-Generation of Hydrogen Peroxide

Supporting Information

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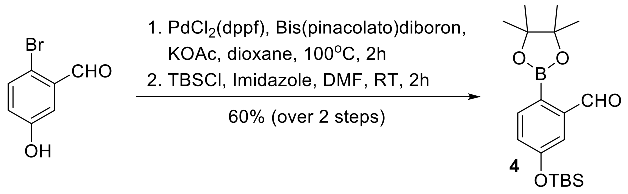
General methods. All reactions requiring anhydrous conditions were performed under an Argon atmosphere. All reactions were carried out at room temperature unless stated otherwise. Chemicals and solvents were either A.R. grade or purified by standard techniques. Thin layer chromatography (TLC): silica gel plates Merck 60 F_{254}: compounds were visualized by irradiation with UV light. Flash chromatography (FC): silica gel Merck 60 (particle size 0.040-0.063 mm), eluent given in parentheses. ^{1}H-NMR spectra were measured using Bruker Avance operated at 400MHz as mentioned. ^{13}C-NMR spectra were measured using Bruker Avance operated at 100 MHz as mentioned. The chemical shifts are expressed in δ relative to TMS (δ = 0 ppm) and coupling constants *J* in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature unless stated otherwise. All general reagents, including salts and solvents, were purchased from Sigma-Aldrich. 4-(tert-Butyldimethylsilyloxy)benzyl bromide was synthesized and exhibited physical properties identical to the literature.

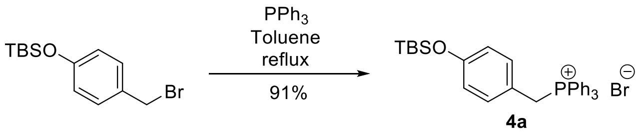
Abbreviations. $PdCl_2$(dppf)-[1,1'-Bis(diphenylphosphino)ferrocence] - dichloropalladium(II), TBSCl- tert-Butyldimethylsilyl chloride *n*-BuLi- *n*-Butyllithium, DCM- Dichloromethane, DMF- N,N'-Dimethylformamide, Et_2O- Diethyl ether, EtOAc- Ethylacetate, Hex- n-Hexane, KOAc- Potassium acetate, , THF- Tetrahydrofuran, PPh_3- Triphenylphosphine.



Compound 4

Commercially available 2-bromo-5-hydroxybenzaldehyde (500 mg, 2.46 mmol) was dissolved in 10 mL of dry dioxane under Ar atmosphere. $PdCl_2$(dppf) (55 mg, 0.08 mmol) was added, followed by Bis(pinacolato)diboron (694 mg, 2.74 mmol) and KOAc (732 mg, 7.46 mmol) and the reaction mixture was heated to 100°C for 2h. After completion, the reaction mixture was diluted with DCM, and was washed with water. The organic layer was separated, dried over Na_2SO_4 and evaporated under reduced pressure. The crude produce was subjected to a short plug of silica gel and eluted with a mixture of EtOAc/Hex (1:3). The solvents were evaporated under reduced pressure and the solid product (413 mg, 67 %) was re-dissolved in 2mL of DMF. Imidazole (172 mg, 2.52 mmol) and TBSCl (315 mg, 2.09 mmol) were added, and the reaction mixture was stirred at room temperature for 2h. After completion, the reaction mixture was diluted with Et_2O, and was washed with saturated NH_4Cl and Brine. The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel and eluted with a mixture of EtOAc/Hex (1:9) to give compound **4** (536 mg, 89%) as colorless oil.

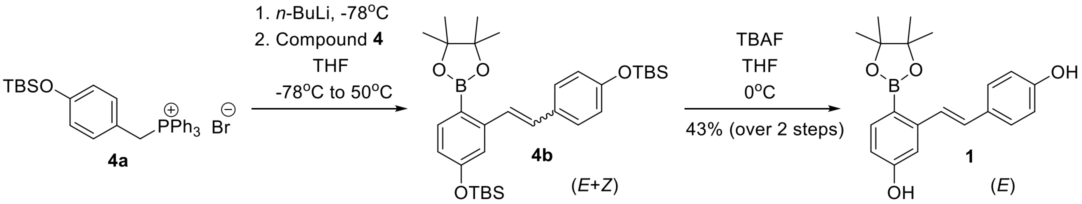
^{1}H NMR (400MHz, $CDCl_3$): $\delta = 10.62$ (1H, s), 7.81 (1H, d, $J = 8.0$ Hz), 7.42 (1H, d, $J = 2.4$ Hz), 7.05 (1H, dd, $J = 8.0, 2.4$ Hz), 1.36 (12H, s), 0.98 (9H, s), 0.21 (6H, s). ^{13}C NMR (100MHz, $CDCl_3$): $\delta = 194.8$, 165.9, 148.1, 137.9, 128.1, 125.1, 118.2, 84.3, 25.7, 25.0, 21.0, -4.3. MS (ESI+): *m/z* calc. for $C_{19}H_{31}BO_4Si$: 362.21; found: 363.27 $[M+H]^+$.



Compound 4a

4-(tert-Butyldimethylsilyloxy)benzyl bromide (3.04 g, 10.09 mmol) was dissolved in 20 mL Toluene, and PPh_3 (2.65 g, 10.09 mmol) in 5 mL Toluene was added dropwise. The reaction mixture was stirred at room temperature for 30 min and then heated to reflux for 2h. After completion, the reaction was cooled to 4°C, filtrated, and the solid was washed with cold Toluene followed by Et_2O, to give compound **4a** (5.2 g, 91%) as a white solid.

^{1}H NMR (400MHz, DMSO-d_6): δ = 7.92-7.88 (3H, m), 7.76-7.71 (6H, m), 7.68-7.63 (6H, m), 6.88-6.85 (2H, m), 6.70 (2H, d, *J* = 8.4 Hz), 5.09 (2H, d, *J* = 15.2 Hz), 0.91 (9H, s), 0.14 (6H, s). ^{31}P NMR (162MHz, DMSO-d_6): δ = 23.4. MS (ESI+): *m/z* calc. for $C_{31}H_{36}OPSi$: 483.23; found: 483.27 $[M]^+$.

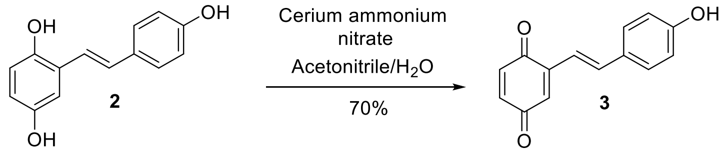


Compound 1

Compound **4a** (480 mg, 0.85 mmol) was suspended in 10 mL of dry THF, and cooled to -78°C under Ar atmosphere. *n*-BuLi (0.34 mL, 0.85 mmol, 2.5M in Hexane) was added dropwise and the mixture was stirred at -78°C for 30 min before compound **4** (280 mg, 0.77 mmol) in 2 mL dry THF was added dropwise. The reaction mixture was stirred at room temperature for 1h and then at 50°C for another 1h until the mixture was homogenous. After completion, the reaction mixture was diluted with Et_2O, and was washed with saturated NH_4Cl and brine. The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was subjected to a short plug of silica gel and eluted with EtOAc/Hex (1:9) to give compound **4b** as a mixture of *E*/*Z* isomers. The mixture was used without further purification. Compound **4b** (192 mg, 0.34 mmol) was dissolved in 2.5 mL dry THF under Ar atmosphere, cooled to 0°C, and TBAF (1.12 mL, 1.12 mmol, 1M in THF) was added dropwise. The reaction mixture was stirred at 0°C for another 15 min before EtOAc was added. The organic layer was washed with saturated NH_4Cl and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel and eluted with EtOAc/Hex (1:4) to give compound **1** (50 mg, 43 % over 2 steps) as pink solid (*E* isomer).

^{1}H NMR (400MHz, $CDCl_3$+MeOD): δ =7.80 (1H, d, *J* = 16.4 Hz), 7.61 (1H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* = 8.4 Hz), 7.11 (1H, d, *J* = 2.4 Hz), 6.88 (1H, d, *J* = 16.4 Hz), 6.77 (2H, d, *J* = 8.4 Hz), 6.65 (1H, dd, *J* = 8.0, 2.4 Hz), 1.31 (12H, s). ^{13}C NMR (100MHz, $CDCl_3$+MeOD): δ =159.3, 156.4, 146.1, 138.2, 130.1, 128.7, 127.9, 126.8, 125.9, 115.6, 113.9, 110.7, 83.5, 24.6. MS (ESI-): *m/z* calc. for $C_{20}H_{23}BO_4$: 338.17; found: 337.19 $[M-H]^-$.

Compound **2** was synthesized and exhibited physical properties identical to the literature. [1]



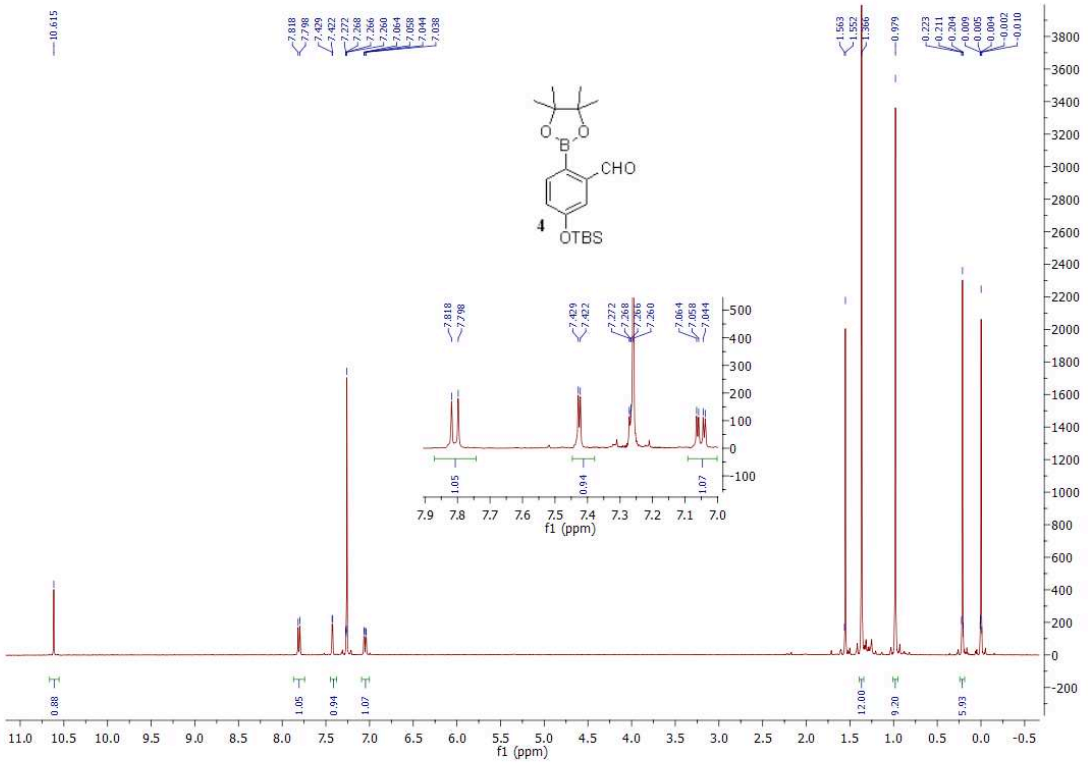
Compound **3**

Compound **2** (100 mg, 0.44 mmol) was dissolved in 1 mL of acetonitrile and cerium ammonium nitrate (483 mg, 0.88 mmol) pre-dissolved in 1 mL of water was addas dropwise at RT. The reaction was stirred for an additional hour at RT. Water was added and the mixture was extracted with DCM. The organic layer was separated, died with Na_2SO_4, filtered and evaporated under reduced pressure to yield compound **3** (70 mg, 70%) as a yellowish solid without further purification.

^{1}H NMR (400MHz, $CDCl_3$): δ =7.58 (2H, d, *J* = 8.8 Hz), 7.18 (1H, d, *J* = 16.4 Hz), 6.84 (1H, d, J = 2.4 Hz), 6.78 (2H, d, *J* = 8.8 Hz), 6.69-6.60 (3H, m).

References

1. R. Csuk, S. Albert, B. Siewert, S. Schwarz, *Eur. J. Med. Chem.*, **2012,** 54, 669-678.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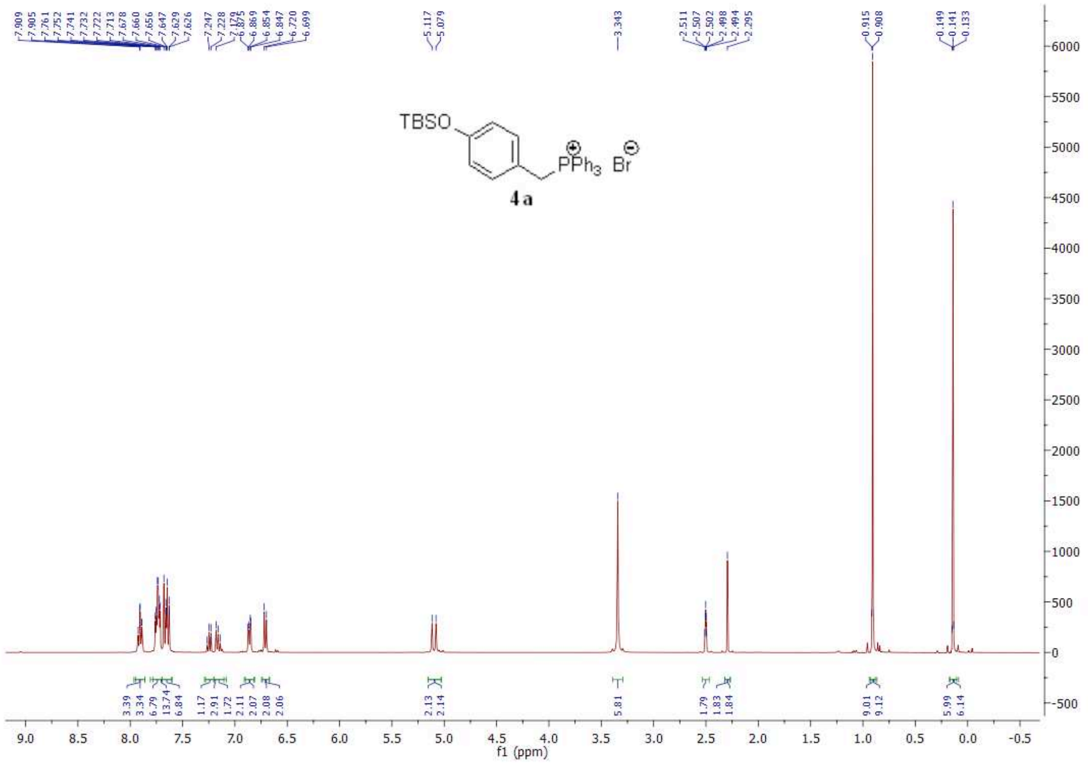
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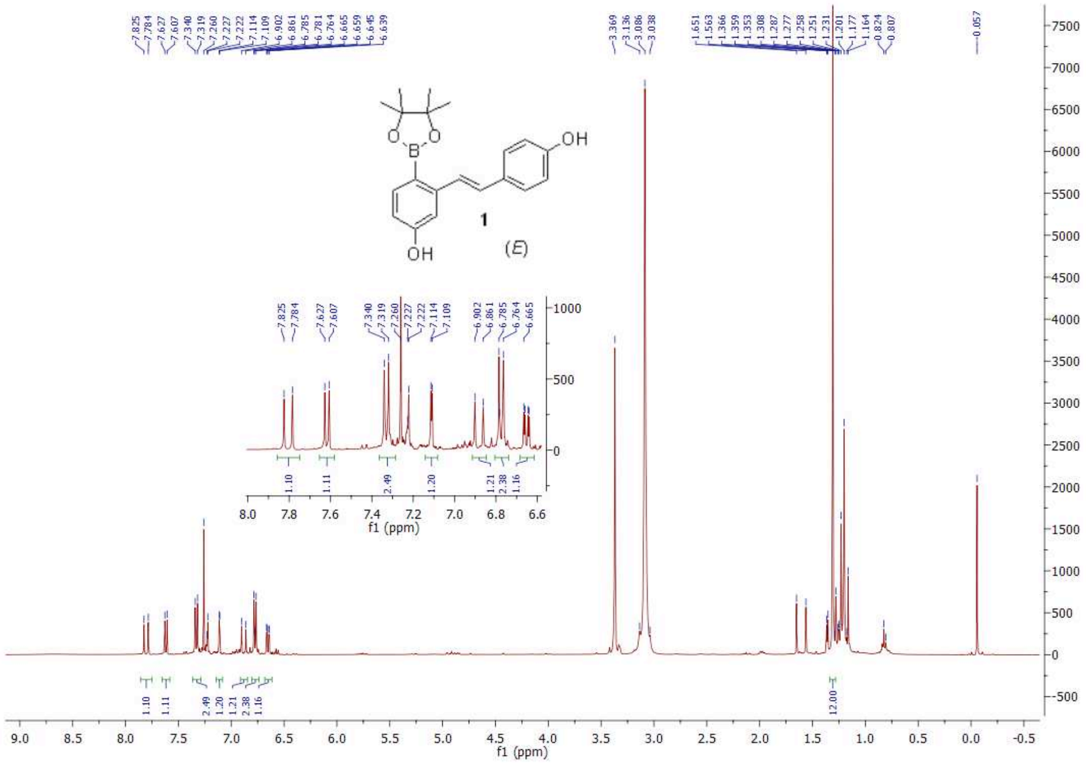
4a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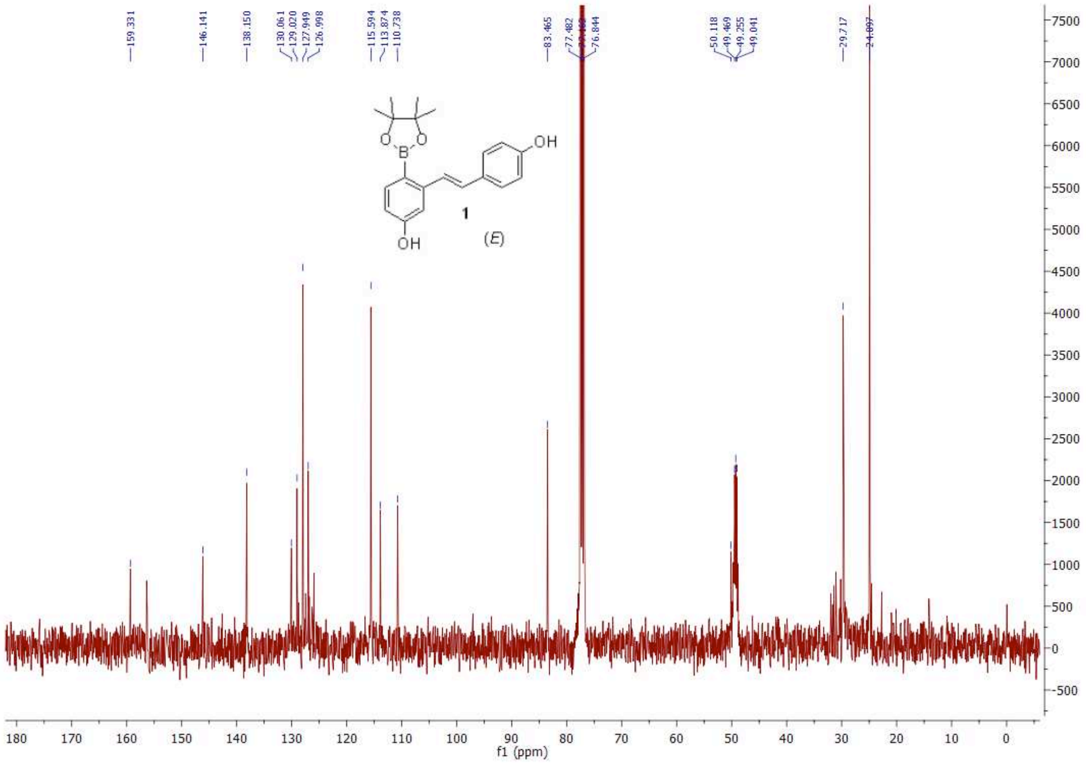
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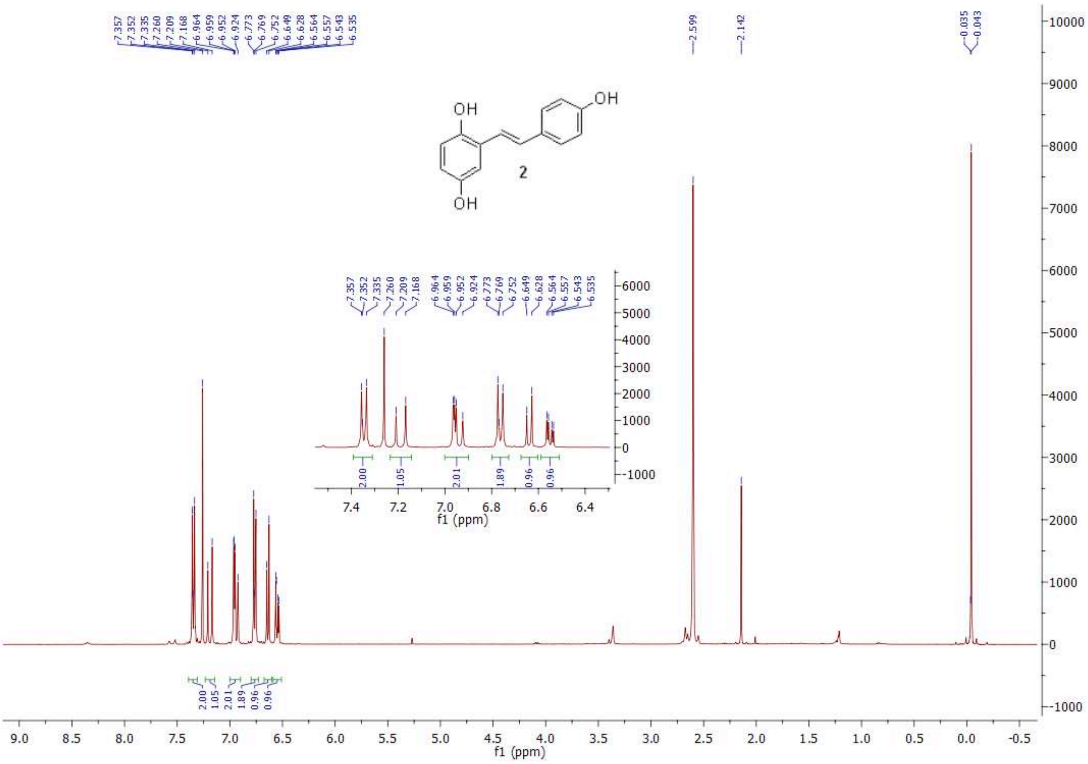
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