Supporting Information

Further Developments of an Enantioselective Palladium-Catalyzed Polyene Cyclization: Surprising Solvent and Ligand Effects

Daniela Lucciola and Brian A. Keay*

Department of Chemistry, University of Calgary, 2500 University Drive NW, Calgary, Alberta, Canada, T2N 1N4.

keay@ucalgary.ca

I. General Experimental Details

All solvents and reagents were purified by standard methods when necessary. Toluene was freshly distilled from CaH$_2$. DME was dried over CaH$_2$, distilled and then dried over Na/benzophenone. Absolute EtOH, DMF, NMP, nitrobenzene, 2-propanol, t-BuOH, and PMP were used without further purification. Pd$_2$(dba)$_3$ and the bisphosphine ligands were stored and dispensed in a glove box. All anhydrous reactions were carried out under an inert atmosphere of N$_2$ or Ar. The glassware used for anhydrous reactions was either dried overnight in an oven at 120 °C or flame-dried.

HPLC analyses were performed on a Chiralcel OD column with UV detection at 254 nm. Flash column chromatography was carried out on a support of Silica gel with a particle size of 40-63 μm (230-400 mesh).

The microwave reactions were performed in a CEM Discover microwave with a magnetron frequency of 2455 MHz. The temperature of the reaction mixture in the microwave was monitored and by a non-contact, infrared sensor located below the microwave cavity floor underneath the reaction vessel. The sensor is vessel volume independent and used in a feedback loop with an on-board computer to control the temperature rise rate and the control point of the vessel contents.

II. General Procedure for the Polyene Cyclization of Trflate 4 in an Oil Bath

Pd$_2$(dba)$_3$ (5.0 mg, 5.0 x 10$^{-3}$ mmol) and bisphosphine ligand (2.00 x 10$^{-2}$ mmol) were weighed into a screw-cap vial, dissolved in the chosen solvent (1.00 mL), and stirred for 30 min at room temperature under an Ar atmosphere. A solution of the triflate 4 (38.5 mg, 0.100 mmol) and PMP (0.09 mL, 0.5 mmol) in the chosen solvent (1.00 mL) was added to the vial containing the catalyst. The vial was then placed in an oil bath.
preheated to 110 °C and allowed to stir for 44 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was filtered through a pipet of silica gel using a 9:1 mixture of hexanes: ethyl acetate as the eluant. A crude 1H NMR was measured to determine the product: starting material: byproduct ratio (P:S:B). Chiral HPLC data: Chiralcel OD, 9:1 hexanes: 2-propanol, \( t_1 = 11.5 \) min (R)-5, \( t_2 = 22.2 \) min (S)-5.

**III. General Procedure for the Polyene Cyclization of Triflate 4 in a Microwave**

Pd\(_{2}\)dba\(_3\) (5.0 mg, 5.0 x 10\(^{-3}\) mmol) and bisphosphine ligand (2.00 x 10\(^{-2}\) mmol) were weighed into a microwave suitable vial, dissolved in the chosen solvent (1.00 mL), and stirred for 30 min at room temperature under an Ar atmosphere. A solution of the triflate 4 (38.5 mg, 0.100 mmol) and PMP (0.09 mL, 0.5 mmol) in the chosen solvent (1.00 mL) was added to the vial containing the catalyst. The vial was then placed in the microwave and the desired temperature and reaction time were programmed. The pressure release was set to 200 psi, the power was set to 115 W, the stirring was activated and the Power Max setting was off. The workup, purification, and HPLC data were identical to that above.

**3-[(t-Butyldimethylsilyl)oxymethyl]furan (20)**

![Chemical structure of 3-[(t-Butyldimethylsilyl)oxymethyl]furan (20)](image)

To a solution of t-butyldimethylsilyl chloride (6.1 g, 40 mmol) in DMF (20 mL) at 0 °C under an atmosphere of Ar was added imidazole (5.7 g, 84 mmol) and 3-hydroxymethylfuran (19, 3.6 g, 37 mmol). After 12 h at 25 °C, diethyl ether and aqueous sodium chloride were added. The organic layer was washed six times with saturated aqueous sodium chloride, dried (Na\(_2\)SO\(_4\)), and the solvent removed in vacuo to afford, after distillation, a clear colourless oil 20 (95%), bp 106-109 °C/20 Torr; IR (neat): 1063 cm\(^{-1}\); 1H NMR (200 MHz) 7.5 (m, 2H), 6.4 (m, 1H), 4.5 (s, 2H), 0.8 (s, 9H), -0.04 (s, 6H), 13C NMR (50 MHz) 143.1, 139.4, 125.9, 109.7, 57.5, 25.8, 18.2, -2.8; mass spectrum, m/z: 212. Anal. calcd. for C\(_{11}\)H\(_{20}\)O\(_2\)Si: C 62.21, H 9.49; found: C 62.34, H 9.43.
2-((1,1-Dimethylethyl)dimethylsilyl)-3-(hydroxymethyl)furan (21)

To a mixture of furan 20 (0.69 g, 3.3 mmol) and HMPA (0.62 mL, 3.6 mmol) dissolved in THF (10 mL) under an atmosphere of Ar at -78 °C was added n-BuLi (1.43 mL, 2.5 M in hexane, 3.6 mmol). The solution was allowed to come to room temperature over 6 h and stirred at room temperature overnight. Saturated ammonium chloride was added and the solution extracted with diethyl ether. The organic layer was washed three times with saturated copper sulfate, dried (Na$_2$SO$_4$), and the solvent removed in vacuo to afford, after distillation, a white crystalline solid 21 (87%), bp 75-78 °C/ 0.02 Torr; IR (KBr): 3319, 155.0, 146.7, 135.9, 1070 cm$^{-1}$; $^1$H NMR (200 MHz) 7.6 (d, 1H, $J =$ 1.8 Hz), 6.5 (d, 1H, $J =$ 1.8 Hz), 4.6 (s, 2H), 1.5 (br s, 1H), 0.9 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR (50 MHz) 155.0, 146.7, 135.9, 110.5, 57.0, 25.7, 18.1, -5.7; mass spectrum, $m/z$: 212. Anal. calcd. for C$_{4}$H$_{20}$O$_{2}$Si: C 62.21, H 9.49; found: C 62.27, H 9.47.

2-((1,1-Dimethylethyl)dimethylsilyl)-4-(propen-2-yl)-3-(hydroxymethyl)furan (22).

Furan 21 (0.71 g, 3.35 mmol) in DME (13 mL) at -78 °C under N$_2$ was treated with n-BuLi (2.5 M in hexane, 2.29 mL, 7.37 mmol). The solution was warmed to 0 °C and stirred for 1 h. B(OMe)$_3$ (0.96 mL, 6.70 mmol) was added and the mixture stirred for 1 h. Into a second flask were placed Pd(PPh$_3$)$_4$ (0.12 g, 0.10 mmol), 2-bromopropene (0.45 mL, 5.03 mmol), and DME (6 mL). The contents of the first flask were transferred by syringe into the second flask followed by the addition of water (3 mL). The flask was immersed into a preheated oil bath at 70 °C. After 1 h diethyl ether was added, the organic layer separated and dried (Na$_2$SO$_4$), and the solvent removed. The crude product was purified by flash chromatography on silica gel using hexane:ethyl acetate (8:1) to provide 22 as a colorless white solid (0.50 g, 59%) which was recrystallized from ethyl
acetate: mp 46-47 °C; IR (neat) 3297, 1471, 1251 cm\(^{-1}\); \(^1\)H NMR (200 MHz) \(7.60\) (s, 1H), 5.41 (br s, 1H), 5.07 (br s, 1H), 4.63 (s, 2H), 2.07 (dd, 3H, \(J = 1.4, 0.7\) Hz), 1.50 (br s, 1H, \(OH\)), 0.93 (s, 9H), 0.33 (s, 6H); \(^13\)C NMR (50 MHz) 157.9, 144.7, 135.2, 133.1, 126.7, 112.9, 55.6, 26.3, 23.5, 17.1, -5.5; mass spectrum, \(m/z\): 252, 237, 195. Anal. Calcd for \(C_{14}H_{24}O_2\)Si: C, 66.61; H, 9.58. Found: C, 66.55; H, 9.85.

3-Formyl-2-((1,1-dimethylethyl)dimethylsilyl)-4-(propen-2-yl)furan (23).

\[
\begin{align*}
\text{OH} & \quad \text{CHO} \\
\text{TBS} & \quad \text{TBS}
\end{align*}
\]

To a flask containing DCM (25 mL) at -78 °C was added oxalyl chloride (1.1 equiv). DMSO (2.2 equiv) was added slowly and the mixture stirred for 2 min. Furan 22 (0.30 g, 1.19 mmol) in DCM (10 mL) was added dropwise over 5 min. After 15 min Et\(_2\)N (5 equiv) was added and the mixture warmed to room temperature. Water (50 mL) was added and the aqueous layer extracted with DCM (5 x 25 mL). The organic layer was washed with 5% HCl (15 mL), 5% Na\(_2\)CO\(_3\) (15 mL), and water (15 mL), dried (Na\(_2\)SO\(_4\)) and the solvent removed to provide 23 as a colorless liquid (0.23 g, 77%): bp 56-70 °C/0.06 Torr; IR (neat) 1690, 1471, 1253 cm\(^{-1}\); \(^1\)H NMR (200 MHz) 10.10 (s, 1H), 7.57 (s, 1H), 5.25 (br s, 1H), 5.13 (br s, 1H), 2.06 (d, 3H, \(J = 0.8\) Hz), 0.95 (s, 9H), 0.37 (s, 6H); \(^13\)C NMR (50 MHz) 186.6, 171.9, 144.6, 135.9, 134.7, 127.1, 115.8, 26.3, 23.3, 17.4, -5.5; mass spectrum, \(m/z\): 250, 235, 193. Anal. Calcd for \(C_{14}H_{22}O_2\)Si: C, 67.15; H, 8.86. Found: C, 66.83; H, 8.93.

3-Ethenyl-2-((1,1-dimethylethyl)dimethylsilyl)-4-(propen-2-yl)-furan (24).

\[
\begin{align*}
\text{CHO} & \quad \text{O} \\
\text{TBS} & \quad \text{TBS}
\end{align*}
\]

Methyltriphenylphosphonium bromide was purified by washing numerous times with hot toluene followed by drying under high vacuum for 8 h. In a nitrogen-purged 3-necked flask, the purified phosphonium salt (0.28 g, 0.77 mmol) was suspended in THF (10 mL) and cooled to 0 °C. \(n\)-BuLi (2.5 M in hexane, 0.14 mL, 0.33 mmol) was added slowly
via a syringe and the reaction mixture warmed to room temperature and allowed to stir for 20 min. A solution of aldehyde 23 (77.6 mg, 0.31 mmol) was dissolved in THF (5 mL) in an addition funnel and added to the orange-yellow solution of the ylide. After refluxing the mixture for 3 h, it was cooled to room temperature, poured into ether (20 mL), and allowed to stir overnight. The solvent was evaporated in vacuo to leave a yellow solid which was purified by flash chromatography on silica gel using hexane:ethyl acetate (100:1) to yield 24 as a colorless liquid (66.6 mg, 87%): bp 38-50 °C/0.06 Torr; IR (neat) 1633, 1251 cm⁻¹; ¹H NMR (200 MHz) 7.48 (s, 1H), 6.67 (dd, 1H, J = 17.9, 11.2 Hz), 5.46 (dd, 1H, J = 17.9, 2.1 Hz), 5.25 (dd, 1H, J = 11.2, 2.1 Hz), 5.15 (br s, 1H), 5.02 (br s, 1H), 2.02 (dd, 3H, J = 1.4, 1.0 Hz), 0.93 (s, 9H), 0.27 (s, 6H); ¹³C NMR (50 MHz) 156.4, 143.7, 136.5, 135.0, 129.1, 126.7, 117.3, 114.0, 26.5, 23.2, 17.7, -5.2; mass spectrum, m/z: 248, 191. Anal. Calcd for C₁₅H₂₄OSi: C, 72.52; H, 9.74. Found: C, 72.46; H, 9.86.

**Preparation of (5-(t-Butyldimethylsilyl)-3-isopropenyl-4-vinyl-2-furyl)-(2-((t-butyldimethylsilyl)oxy)phenyl)methanone (26).**

![Reaction Scheme]

Trisubstituted furan 24 (250 mg, 1 mmol) was dissolved in THF (10 mL) and was cooled to −78 °C. n-BuLi (0.69 mL, 1.6 M in hexanes, 1.1 mmol) was added slowly and the reaction mixture was stirred at −78 °C for 1 h. This anion solution was then added slowly to a −78 °C solution of acid chloride 25 (298 mg, 1.1 mmol) in THF (10 mL) and was stirred at −78 °C overnight. The reaction mixture was diluted with diethyl ether (20 mL) and quenched with 1 M HCl (10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride (3 × 20 mL), dried (MgSO₄) and concentrated in vacuo. The column chromatographed product 26 (100:1 hexanes: ethyl acetate) was a yellow oil (415 mg, 0.86 mmol, 86%). bp 170 °C/0.08 Torr (dec); IR (KBr) 1661 cm⁻¹; ¹H NMR (200 MHz) 7.25-7.35 (m, 2H), 6.98 (dt, J = 1.0, 7.7 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 6.57 (dd, J =
Preparation of (2-Hydroxyphenyl)-(3-isopropenyl-4-vinyl-2-furyl)methanone (27).

Disilane 26 (400 mg, 0.83 mmol) was dissolved in THF (10 mL) and was cooled to 0 °C. TBAF (2.5 mL, 1 M in THF, 2.5 mmol) was added and the solution was stirred at rt for 4 h. The reaction mixture was diluted with diethyl ether (10 mL) and quenched with 1 M HCl (10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the organic layers were combined. The organic layer was washed with saturated aqueous sodium chloride (3 × 20 mL), dried (MgSO₄) and concentrated in vacuo to afford a yellow oil. The crude product was purified via column chromatography (100:1 hexanes: ethyl acetate) to give a yellow solid 27 (209 mg, 0.82 mmol, 99%). Mp 55-58 °C; bp 105-115 °C/0.08 Torr; IR (KBr) 3139, 1624 cm⁻¹; ¹H NMR (200 MHz) 12.2 (s, 1H), 8.24 (dd, J = 1.7, 7.5 Hz, 1H), 7.73 (s, 1H), 7.40-7.50 (m, 1H), 6.85-7.05 (m, 2H), 6.46 (dd, J = 11.5, 17.6 Hz, 1H), 5.65 (dd, J = 1.9, 17.6 Hz, 1H), 5.30-5.40 (m, 1H), 5.24 (dd, J = 1.9, 11.5 Hz, 1H), 4.95-5.05 (m, 1H), 2.00-2.10 (m, 1H); ¹³C NMR (50 MHz) 185.9, 163.4, 147.4, 141.9, 136.8, 136.6, 135.9, 132.0, 126.3, 125.0, 119.1, 118.7, 118.2, 117.2, 116.5, 22.9. mass spectrum, m/z: 254, 239, 121. Exact mass for C₁₆H₁₄O₃ (M⁺): calcd 254.0943, found 254.0922. Anal. for C₁₆H₁₄O₃: calcd C 75.58, H 5.55; found C 75.64, H 5.57 %.

Preparation of 2-(3-Isopropenyl-4-vinylfuran-2-carbonyl)phenyl (Trifluoromethane)sulfonate (4).
Phenol 27 ((100 mg, 0.39 mmol) was dissolved in DCM (5 mL) and cooled to –45 °C. Et₃N (0.15 mL, 1.1 mmol) was added and then triflic anhydride (93 μL, 0.55 mmol) was added slowly and the mixture was allowed to warm to room temperature and stirred for 15 minutes forming a pink solution. The reaction was diluted with DCM (5 mL) and quenched with 10% HCl (1 mL). The organic layer washed with saturated aqueous sodium chloride (3 × 5 mL), dried (MgSO₄) and concentrated in vacuo to afford a pink oil which was purified by column chromatography (50:1 hexanes: ethyl acetate) to give 4 as a pale yellow oil (140 mg, 0.36 mmol, 92%). Due to its instability, it was used immediately in the next reaction. ¹H NMR (200 MHz) 7.63 (s, 1H), 7.30-7.70 (m, 4H), 5.25-5.40 (m, 1H), 5.26 (dd, J = 1.4, 11.3 Hz, 1H), 5.63 (dd, J = 11.3, 17.9 Hz, 1H), 4.95-5.05 (m, 1H), 2.00-2.10 (m, 3H).

**Preparation of 10b-Methyl-1,10b-dihydro-5-oxa-acephenanthrylen-6-one (5) and By-Product 6.**

Pd₂dba₃ (5.0 mg, 5.0 x 10⁻³ mmol) and (R)-BINAP (2.00 x 10⁻² mmol) were weighed into a screw-cap vial, dissolved in toluene (1.00 mL), and stirred for 30 min at room temperature under an Ar atmosphere. A solution of the triflate 4 (39.7 mg, 0.103 mmol) and PMP (0.09 mL, 0.5 mmol) in toluene (1.00 mL) was added to the vial containing the catalyst. The vial was then placed in an oil bath preheated to 110 °C and allowed to stir for 44 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was filtered through a pipet of silica gel using a 9:1 mixture of hexanes: ethyl acetate as the eluant. A crude ¹H NMR was measured to
determine the product: starting material: byproduct ratio (P:S:B). This material was then further purified by flash column chromatography (9:1 hexanes: ethyl acetate) to furnish a yellow solid 5 (22.0 mg, 0.093 mmol, 91%) and trace amounts 6. Chiral HPLC data on 5: Chiralcel OD, 9:1 hexanes: 2-propanol, t₁ = 11.5 min (R)-5, t₂ = 22.2 min (S)-5: 72% ee.

**Compound 5:** IR (KBr) 1671 cm⁻¹; ¹H NMR (200 MHz) 8.37 (dd, J = 0.7, 1.5, 7.6 Hz, 1H), 7.56 (s, 1H), 7.40-7.65 (m, 3H), 6.62 (ddd, J = 0.7, 3.2, 9.7 Hz), 6.07 (ddd, J = 2.4, 6.2, 9.7 Hz), 2.95 (ddd, J = 0.7, 6.2, 16.6 Hz, 1H), 1.48 (s, 3H), 2.53 (m, 1H). ¹³C NMR (50 MHz) 172.5, 149.9, 144.1, 143.9, 141.3, 133.4, 132.1, 128.3, 128.0, 127.0, 125.1, 120.8, 117.7, 35.3, 34.6, 31.1. mass spectrum, m/z 236, 221, 208, 193. Exact mass for C₁₆H₁₂O₂ (M⁺): calcd 236.0837, found 236.0829.

**Compound 6:** IR (KBr) 1718 cm⁻¹; ¹H NMR (200 MHz) 8.30-8.40 (m, 1H), 7.82 (s, 1H), 7.60-7.70 (m, 2H), 7.35-7.50 (m, 1H), 6.76 (dd, J = 10.9, 17.4 Hz, 1H), 5.61 (dd, J = 1.4, 17.4 Hz, 1H), 5.37 (dd, J = 1.4, 10.9 Hz, 1H), 1.72 (s, 6H). ¹³C NMR (50 MHz) 195.0, 151.0, 146.0, 144.6, 142.0, 132.6, 131.2, 126.9, 126.8, 126.3, 125.8, 125.1, 117.7, 37.9, 29.1. mass spectrum, m/z: 238, 223. Exact mass for C₁₆H₁₄O₂ (M⁺): calcd 238.0994, found 238.1003.
$^1$H NMR Spectrum of 5
$^{13}$C NMR Spectrum of 5