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Nazarov Cylisations without Lewis Acids

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Supporting Information

General Procedures

NMR spectra were recorded on a Brüker AC250 (250MHz) instrument. The ^{1}H data is presented as follows: chemical shift (in ppm on the δ scale), integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet,) and the coupling constant (J, in hertz). The ^{13}C data is reported as the ppm on the δ scale followed by the interpretation. IR spectra were recorded on a JASCO FT/IR-460 plus instrument using 4mm sodium chloride disks. The wavelengths of the maximum absorbance (ν_{max}) are quoted in cm^{-1}. Mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea. Accurate mass measurements were obtained on a Finnigan MAT 900 XLT double focusing mass spectrometer. The data is recorded as the ionisation method followed by the calculated and measured masses.

TLC was performed on Merck $60F_{254}$ silica plates and visualised by UV light and/or anisaldehyde or potassium permanganate stains. The compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure. The eluent is quoted as a percentage.

All solvents were dried before use unless other wise stated. THF was dried over sodium with benzophenone as an indicator. DCM was distilled over calcium hydride. Diisopropylamine and pyridine were dried and stored over potassium hydroxide. N, N-dimethylacetamide (DMA) was distilled at 42°C, 0.8 mBar from CaH_2, and stored over 3Å molecular sieves under nitrogen.

All other chemicals were purchased from a chemical supplier and used as received.

Synthesis of starting dienones

Dienones **1**,[1] **3**,[2] **4**,[3] **5 – 6**[4] and **11**[5] were prepared according to literature procedures. The remaining dienones were synthesised through the addition of 2-lithiodihydropyran to the appropriate morpholine amide using the following procedure:[4]

To 2,4 dihydropyran (1mL, 11.0 mmol) in THF (0.45 mL) at -78°C was added *tert*-butyllithium (6.5 mL, 1.7 M in pentane, 11.0 mmol) and the reaction mixture was allowed to warm to -5°C over 1 h. The reaction mixture was then cooled to -78°C and the morpholine amide (8.6 mmol) in THF (10 mL) was added via canula and the reaction mixture was stirred for 1 h at -78°C. The reaction mixture was quenched with brine / diethyl ether (75 / 20 mL), extracted with diethyl ether (3 x 40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane : diethyl ether = 9:1) to afford the dienone in 27-56% yield.

1-(5,6-Dihydro-4*H*-pyran-2-yl)-2-methyl-pent-2-en-1-one, **7**. Yellow oil; IR(thin film/cm^{-1}): ν_{max} 2933, 1651, 1286, 1064, 917; ^{1}H-NMR($CDCl_3$, 250 MHz) δ 6.36 (1H, td, J = 6.0. 1.3Hz), 5.65 (1H, t, J = 4.1Hz), 4.11 (2H, t, J = 5.2Hz), 2.17-2.26 (4H, m), 1.83–1.87 (2H, m), 1.83 (3H, s), 1.05 (3H, t, J = 7.4Hz); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 193.20, 151.09, 144.25, 134.38, 111.96, 66.10, 21.87, 21.39, 20.56, 12.87, 12.40; HRMS (ES^+): calcd for $C_{11}H_{16}O_2$ $[M+H]^+$:181.1223, found: 181.1223.

1-(5,6-Dihydro-4*H*-pyran-2-yl)-2-methyl-3-phenyl-but-2-en-1-one, **8**. Colourless oil, 5:1 mixture of *E* and *Z* isomers. IR(thin film/cm^{-1}): ν_{max} 2933, 2873, 1667, 993, 904, 703; ^{1}H-NMR($CDCl_3$, 250 MHz) δ 7.19-7.37 (6H, m), 6.14 (1H, t, J = 4.2Hz), 5.60 (0.2H, t, J = 4.0Hz), 4.17 (2H, t, J = 5.3, Hz), 3.70 (0.4H, t, J = 5.2Hz), 2.20 – 2.25 (2.4H, m), 2.08 (0.6H, q J = 1.1Hz), 1.94 (0.6H, q, J = 1.1Hz), 1.65-1.90 (2.4H, m), 1.85 (3H, q, J = 1.5Hz), 1.77 (3H, q, J = 1.5Hz); ^{13}C-NMR ($CDCl_3$, 63 MHz) (major *E* isomer only) δ 196.52, 150.75, 141.79, 136,40, 131.08, 128.11, 127.73, 126.85, 116.15, 66.33, 22.15, 21.07, 20.40, 18.05; HRMS (ES^+): calcd for $C_{16}H_{18}O_2$ $[M+H]^+$:243.1380, found: 243.1380.

1-(5,6-Dihydro-4*H*-pyran-2-yl)-2,3-diphenyl-propenone, **9**. Yellow solid, 7:3 mixture of *E* and *Z*-isomers; IR (thin film/cm^{-1}): ν_{max} 2932, 2359, 1624, 1070, 931, 765, 694; ^{1}H-NMR($CDCl_3$, 250 MHz) *E* isomer: δ 6.91-8.09 (11H, m), 5.77 (1H, t, J = 4.1Hz), 3.79-3.94 (2H, m), 1.99-2.06 (2H,

m); 1.61–1.71 (2H, m); *Z* isomer: δ 6.91-8.09 (11H, m), 5.83 (1H, t, J = 4.2Hz), 3.79-3.94 (2H, m), 1.80-1.85 (2H, m); 1.51–1.55 (2H, m); ^{13}C-NMR ($CDCl_3$, 63 MHz) major *E* isomer only: δ 192.06, 151.53, 139.83, 136.85, 136.28, 134.82, 130.04, 129.26, 128.70, 128.49, 128.04, 127.68, 114.71, 66.17, 21.35, 20.89; HRMS (EI^+): calcd for $C_{20}H_{18}O_2$ [M^+]: 290.13068, found: 290.13038.

(5,6-Dihydro-4H-pyran-2-yl)-(3,4,5-trimethoxy-phenyl)-methanone, **10**. White solid; M.p. = 59°C (hexane/diethyl ether); IR(thin film/cm^{-1}): ν_{max} 2938, 1582, 1329, 1126, 1002, 731; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.07 (2H, s), 5.85 (1H, t, J = 4.2Hz), 4.20 (2H, t, J = 5.1Hz), 3.90 (9H, s), 2.31-2.47 (2H, m), 2.16-2.07 (2H, m); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 189.65, 152.42, 151.17, 141.53, 131.93, 114.46, 106.89, 66.22, 60.65, 56.03, 21.26, 20.73; HRMS (ES^+): calcd for $C_{15}H_{18}O_5$ $[M+H]^+$:279.1227, found: 279.1228.

General procedure for microwave-assisted Nazarov cyclisations.

All microwave irradiations were carried out in a CEM Discover microwave equipped with an Explorer module controlled by an external computer. A solution of the dienone (0.4 – 0.83mmol) in DMA or $EMImBF_4$ (0.5mL) was made up in a microwave vessel equipped with a stirrer bar. The mixture was stirred and irradiated under the following conditions: $EMImBF_4$: μpower = 100W, pressure = 100psi, ramp time = 1min, hold time = 2min, temperature = 250°C. DMA: μpower = 300W, pressure = 300psi, ramp time = 5min, hold time = 30min, temperature = 180°C. Reaction times are listed separately for each compound.
The reaction mixture was quenched with diethyl ether (20 mL), filtered through celite and absorbed onto silica gel (1.0 g). Flash column chromatography using hexane/diethyl ether mixtures gave the pure cyclopentenone in 56-98% yield.
Cyclopentenones **2**[1] ($EMImBF_4$, 2min), **12**[6] (**(**$EMImBF_4$, 3min), **13**[7] ($EMImBF_4$, 2min) and **15**[1] (DMA, 15min) have been previously described in the literature.

5-Ethoxy-3-ethyl-2-methyl-cyclopent-2-enone, **14**, (DMA, 45 min).

Pale yellow oil; IR(thin film/cm^{-1}): ν_{max} 2933, 1708, 1644, 1347, 1124, 930; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 3.77–3.91 (2H, m), 3.51-3.64 (2H, m), 2.77 (1H, dd, J = 17.6, 7.0Hz), 2.26-2.45 (2H, m), 1.62 (3H, t, J = 2.0Hz), 1.17 (3H, t, J = 7.0Hz), 1.05 (3H, t, J = 7.6Hz); ^{13}C-NMR ($CDCl_3$, 63

MHz) δ 206.8, 171.6, 133.7, 77.1, 65.6, 36.0, 24.0, 15.1, 11.1, 7.5; HRMS (ES^+): calcd for $C_{10}H_{20}NO_2$ $[M+NH_4]^+$:186.1489, found: 186.1488.

5-Ethyl-6-methyl-3,4,5,6-tetrahydro-2*H*-cyclopenta[b]pyran-7-one, **16**, (DMA, 30 min).

Colourless oil, 9:1 mixture of diastereoisomers (unassigned). IR(thin film/cm^{-1}): ν_{max} 2929, 1706, 1647, 1456, 1296, 1122, 976; ^{1}H-NMR ($CDCl_3$, 250 MHz) (major diastereoisomer) δ 4.20-4.40 (2H, m), 2.30 (1H, m), 2.05-2.17 (2H, m), 1.82-1.90 (3H, m), 1.68 (1H, m), 1.22 (1H, m), 1.09 (3H, d, J = 7.5Hz), 0.84 (3H, t, J = 7.4Hz); ^{13}C-NMR ($CDCl_3$, 63 MHz) (major diastereoisomer) δ 202.66, 149.47, 146.54, 66.38, 47.48, 43.81, 24.94, 22.60, 22.08, 15.90, 11.02; HRMS (ES^+): calcd for $C_{11}H_{20}NO_2$ $[M+NH_4]^+$:198.1489, found: 198.1487.

5,6-Dimethyl-5-phenyl-3,4,5,6-tetrahydro-2*H*-cyclopenta[b]pyran-7-one, **17**, (DMA, 15 min).

Colourless oil, 1:1 mixture of diastereoisomers (unassigned). IR(thin film/cm^{-1}): ν_{max} 2932, 1713, 1649, 1444, 1267, 970, 702; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 6.99-7.69 (10H, m), 4.17-4.33 (4H, m), 1.99-2.51 (10H, m), 1.73 (3H, s), 1.53 (3H, s), 1.18 (3H, d, J = 7.4Hz), 0.68 (3H, d, J = 7.4Hz); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 202.17, 202.09, 150.40, 150.19, 149.85, 148.58, 145.03, 141.87, 128.57, 128.12, 126.87, 126.48, 126.36, 125.79, 66.75, 66.69, 54.07, 52.27, 48.25, 47.47, 23.79, 21.48, 20.21, 19.64, 11.18, 9.57; HRMS (ES^+): calcd for $C_{16}H_{22}NO_2$ $[M+NH_4]^+$:260.1645, found: 260.1643.

trans-5,6-Diphenyl-3,4,5,6-tetrahydro-2*H*-cyclopenta[b]pyran-7-one, **18**, (DMA, 45 min).

White solid; M.p. = 136.2°C (hexane/diethyl ether); IR(thin film/cm^{-1}): ν_{max} 3027, 1713, 1649, 1121, 1068, 699; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.42-7.82 (8H, m), 6.95-7.29 (2H, m), 4.32-4.71 (2H, m), 3.96 (1H, d, J = 1.8Hz), 3.59 (1H, d, J = 1.8Hz), 2.25-2.32 (4H, m); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 199.61, 150.83, 146.16, 140.54, 138.40, 128.93, 128.68, 127.80, 127.20, 127.00, 66.92, 60.23, 54.29, 22.08, 21.39; HRMS (EI^+): calcd for $C_{16}H_{18}O_2$ $[M]^+$: 290.13068, found: 290.13059.

*Nazarov cyclisation of dienone **6** in the presence of proton sponge*

A base-washed (KOH/EtOH) microwave vessel was charged with a solution of the dienone **6** (50 mg, 0.26 mmol) and (1-8-Bis(dimethylamino)-naphtalene (proton sponge) (56 mg, 0.26 mmol) in freshly distilled, dry DMA (0.5 mL). The reaction mixture was stirred and heated under microwave irradiation for 30 min. at 180 °C, then diluted with diethyl ether (20 mL) and quenched with aqueous HCl solution (1M, 20 mL). The organic phase was separated, filtered and concentrated on silica gel (1.0 g). The product was purified by column chromatography (hexane : ether = 6:4) to afford 30 mg (60%) of *cis*-3,4,4b,5,6,7,8,8a-octahydro-2*H*-1-oxa-fluoren-9-one,[1] **15** as a colorless oil. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 3.99-4.07 (2H, m), 2.67 (1H, m), 2.11-2.40 (3H, m), 1.60-1.93 (5H, m), 1.07-2.49 (5H, m).

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