ELECTRONIC SUPPLEMENTARY INFORMATION

Regioselectivity in the Sonogashira coupling of 4,6-dichloro-2-pyrone

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1.0 Synthetic details (procedures and characterisation data)

The following characterisation data was checked using the *Experimental data checker* developed by Goodmann, Kidd, Murray-Rust and co-workers.[S1]

4,6-Dichloro-2-pyrone (8)

Compound **8** was prepared according to the procedure described by Afarinkia and co-workers in 65% yield as a pale white solid.[S2] Mp 44-46 ºC, Lit. 43-45 ºC; δ_H (400 MHz, $CDCl_3$, ppm) 6.31 (s, 2H); LRCI *m/z* 164 (M^+, 55), 129 (M^+-Cl, 100).

4-Chloro-6-(*N*-diethylamino)-2-pyrone (12)

Isolated as a viscous oil. δ_H (400 MHz, $CDCl_3$, ppm) 5.45 (d, 1H, ^4J=1.6Hz), 5.18 (d, 1H, ^4J=1.6Hz), 3.39 (q, 4H, ^3J=7.1Hz), 1.23 (t, 6H, ^3J=7.1Hz); δ_C (100 MHz, $CDCl_3$) 160.6, 134.6, 127.7, 93.6, 82.3, 42.7, 12.5; ν_{max} (CH_2Cl_2, cm^{-1}) 1726 (C=O), 1585 (C=C), 1531; LRCI *m/z* 202 (MH^+, 100), 218 ($M+NH_4^+$, 60); HRCI *m/z* exact mass calcd. for $C_9H_{13}NO_2Cl$ (MH^+): 202.06348, found: 202.06344 (0.2 ppm error).

General procedure for Sonogashira cross-coupling

To a degassed solution containing compound **8** (0.38 mmol, 1 equiv.) and the terminal acetylene (0.42 mmol, 1.1 equiv) in dry toluene (2 mL) under a nitrogen atmosphere, was added Et_3N (0.16 ml, 1.15 mmol, 3 equiv.), followed by $Pd(PPh_3)_2Cl_2$ (1.3 mg, 1.9 μmol,

5 mol%) and CuI (0.2 mg, 1.1 μmol, 3 mol%). The solution was allowed to stir for 21 hours at 25 ºC. After this time, the mixture was concentrated *in vacuo* and the resultant oil purified by column chromatography on silica-gel using hexane/ethyl acetate mixtures (9:1 to 7:3), which gave the cross-coupled products as crystalline solids or viscous oils.

4-Chloro-6-(2-phenylethynyl)-2-pyrone (9a)

The *title compound* is a crystalline yellow solid. Mp 97-98°C; δ_H (400 MHz, $CDCl_3$, ppm) 7.52 (m, 3H), 7.40 (m, 2H), 6.51 (d, 1H, ^4J=1.7Hz) 6.41 (d, 1H, ^4J=1.7Hz); δ_C (400 MHz, $CDCl_3$, ppm) 160.6, 151.2, 144.3, 132.0, 128.6, 121.0, 120.5, 117.5, 112.0, 95.9, 81.3; ν_{max} (CH_2Cl_2, cm^{-1}) 2210 (C≡C), 1728 (C=O), 1618 (C=C), 1531; LRCI *m/z* 231 (MH^+, 100), 248 ($M+NH_4^+$, 73); HRCI *m/z* exact mass calcd. for $C_{13}H_{11}NO_2Cl$ ($M+NH_4^+$): 248.04785, found: 248.04780 (0.1 ppm error).

4-Chloro-6-(pent-1-ynyl)-2-pyrone (9b)

The *title compound* is a yellow oil. δ_H (400 MHz, $CDCl_3$, ppm) 6.36 (d, 1H, ^4J=1.8Hz) 6.34 (d, 1H, ^4J=1.8Hz), 2.41 (t, 2H, ^3J=7.0Hz), 1.63 (m, 2H), 1.02 (t, 3H, ^3J=7.4Hz); δ_C (100 MHz, $CDCl_3$, ppm) 159.3, 150.6, 143.9, 115.4, 112.7, 95.5, 82.9, 27.7, 21.0, 14.1; ν_{max} (CH_2Cl_2, cm^{-1}) 2966, 2935, 2873, 2229 (C≡C), 1728 (C=O), 1620, 1531, 1462, 1383, 1263; LRCI *m/z* 197 (M^+, 66), 214 ($M+NH_4^+$, 100); HRCI *m/z* exact mass calcd. for $C_{10}H_{13}NO_2Cl$ ($M+NH_4^+$): 214.06299, found 214.06336 (0.5 ppm error).

4-Chloro-6-(hex-1-ynyl)-2-pyrone (9c)

The *title compound* is a brown oil. δ_H (400 MHz, $CDCl_3$, ppm) 6.34 (d, 1H, ^4J=1.8Hz), 6.32 (d, 1H, ^4J=1.8Hz), 2.42 (t, 2H, ^3J=7.0Hz), 1.56 (m, 2H), 1.43 (m, 2H), 0.92 (t, 3H, ^3J=7.3 Hz); δ_C (100 MHz, $CDCl_3$, ppm) 159.9, 150.9, 144.8, 113.9, 111.4, 100.1, 72.8, 30.0, 21.9, 19.3, 13.5; ν_{max} (CH_2Cl_2, cm^{-1}) 2962, 2936, 2873, 2227 (C≡C), 1723(C=O), 1618, 1531, 1532, 1467, 1383, 1275; LRCI *m/z* 211 (MH^+, 100), 228 ($M+NH_4^+$, 50); HRCI *m/z* exact mass calcd. for $C_{11}H_{15}NO_2Cl$ ($M+NH_4^+$): 228.07913, found: 228.07886 (1.2 ppm error).

4-Chloro-6-(trimethylsilyl)-2-pyrone (9d)

The *title compound* is a brown oil. δ_H (400 MHz, $CDCl_3$, ppm) 6.50 (d, 1H, ^4J=1.8Hz), 6.46 (d, 1H, ^4J=1.8Hz), 0.06 (m, 9H); ν_{max} (CH_2Cl_2, cm^{-1}) 3020, 2960, 2254 (C=C), 1730 (C=O), 1606, 1535, 1265, 1095, 921; LRCI *m/z* 227 (MH^+, 100), 244 ($M+NH_4^+$, 50); HRCI *m/z* exact mass calcd. for $C_{10}H_{12}O_2SiCl$: 227.02951, found 227.02880 (3.1 ppm error). Note: This compound degrades readily in common organic solvents. Desilylation appears to occur on prolonged exposure to silica-gel during chromatography which gives 4-chloro-6-(eth-1-ynyl)-2-pyrone. δ_H (400 MHz, $CDCl_3$) 6.40 (d, 1H, ^4J=1.8Hz), 6.43 (d, 1H, ^4J=1.8Hz), 3.42 (s, 1H).

4-Chloro-6-(2-(*p*-methylphenyl)ethynyl)-2-pyrone (9e)

The *title compound* is a brown oil. δ_H (400 MHz, $CDCl_3$, ppm) 7.44 (d, 2H, ^3J=7.9Hz), 7.20 (d, 2H, ^3J=7.9Hz), 6.48 (d, 1H, ^4J=1.8Hz), 6.39 (d, 1H, ^4J=1.8Hz), 2.39 (s, 3H); δ_C (100 MHz, $CDCl_3$, ppm) 160.1, 151.2, 145.1, 141.4, 132.4, 129.8, 117.3, 114.4, 112.1, 97.9, 80.6, 22.0; ν_{max} (CH_2Cl_2, cm^{-1}) 3072, 2983, 2234 (C≡C), 1738 (C=O), 1602, 1537, 1475, 1113; LREI *m/z* 244 (M^+, 46), 216 (M^+-CO, 100); HRCI *m/z* exact mass calcd. for $C_{14}H_9O_2Cl$: 244.02911, found: 244.02911 (0.0 ppm error).

4-Chloro-6-(2-(*p*-methoxyphenyl)ethynyl)-2-pyrone (9f)

The *title compound* is a dark brown oil. δ_H (400 MHz, $CDCl_3$, ppm) 7.48 (d, 2H, ^3J=8.9), 6.91 (d, 2H, ^3J=8.9), 6.47 (d, 1H, ^4J=1.8Hz), 6.38 (d, 1H, ^4J=1.8Hz), 3.84 (s, 3H); δ_C (100 MHz, $CDCl_3$, ppm) 161.4, 159.8, 151.3, 144.5, 133.9, 114.4, 113.8, 111.9, 111.5, 98.1, 80.0, 55.4; ν_{max} (CH_2Cl_2, cm^{-1}) 3068, 2935, 2206(C≡C), 1738(C=O), 1599, 1537, 1358, 1294, 1252; LREI *m/z* 260 (M^+, 100); HREI *m/z* exact mass calcd. for $C_{14}H_9O_3Cl$: 260.02402, found: 260.02406 (-0.1 ppm error).

4-Chloro-6-(2-(*p*-acetylphenyl)ethynyl)-2-pyrone (9g)

The *title compound* is a brown oil. δ_H (400 MHz, $CDCl_3$, ppm) 7.96 (d, 2H, ^3J=8.5Hz), 7.62 (d, 2H, ^3J=8.5Hz), 6.54 (d, 1H, ^4J=1.8Hz), 6.43 (d, 1H, ^4J=1.8Hz), 2.60 (s, 3H); δ_C (400 MHz, $CDCl_3$, ppm) 197.0, 161.2, 159.4, 150.7, 144.0, 132.5, 128.5, 127.5, 115.1, 112.9, 95.6, 83.1, 26.6; ν_{max} (CH_2Cl_2, cm^{-1}) 2964, 2840, 2206(C≡C), 1734 (C=O), 1535,

1358, 1294, 1252; LRCI *m/z* 273 (MH^+, 45), 290 ($M+NH_4^+$, 100). HREI *m/z* exact mass calcd. for $C_{15}H_{13}NO_3Cl$: 290.05839, found: 290.05799 (1.4 ppm error).

4-Chloro-6-(2-(*p*-nitrophenyl)ethynyl)-2-pyrone (9h)

The *title compound* is a yellow solid. Mp 170-172°C. δ_H (400 MHz, $CDCl_3$, ppm) 8.27 (d, 1H, ^3J=8.9Hz), 7.72 (d, 1H, ^3J=8.9Hz), 6.59 (d, 2H, ^4J=1.8Hz), 6.48 (d, 2H, ^4J=1.8Hz); δ_C (100 MHz, $CDCl_3$, ppm) 159.1, 150.5, 148.3, 143.5, 133.0, 126.7, 123.9, 115.5, 113.3, 93.9, 84.6; ν_{max} (CH_2Cl_2, cm^{-1}) 2960, 2925, 2856, 2212 (C≡C), 1741(C=O), 1610, 1538, 1346, 1255; LREI *m/z* 275 (M^+, 56), 247 (M^+-CO, 100); HRCI *m/z* exact mass calcd. for $C_{13}H_6O_4NCl$: 274.99854, found: 274.99841 (0.5 ppm error).

4-Chloro-6-(2-(ferrocenyl)ethynyl)-2-pyrone (9i)

The *title compound* is a dark red solid. Mp 186-188 °C; δ_H (400 MHz, $CDCl_3$, ppm) 6.43 (d, 1H, ^4J=1.7Hz) 6.38 (d, 1H, ^4J=1.7Hz), 4.56 (m, 2H), 4.37 (m, 2H), 4.27 (s, 5H); δ_C (100 MHz, $CDCl_3$, ppm) 160.0, 151.1, 145.1, 113.3, 110.9, 99.1, 77.6, 72.2, 70.4, 70.3, 60.9; ν_{max} (CH_2Cl_2, cm^{-1}) 3066, 2976, 2906, 2210 (C≡C), 1741 (C=O), 1604, 1537, 1456, 1263; LREI *m/z* 338 (M^+, 100), 310 (M^+-CO, 23), 273 (M^+-C_5H_5, 12); HRCI *m/z* exact mass calcd. for $C_{17}H_{11}O_2FeCl$ (M^+): 337.97969, found: 337.97962 (0.2 ppm error).

2.0 Theoretical studies

Geometry optimisations were performed using density functional theory calculations at the Becke3LYP (B3LYP) level.[S3] Frequency calculations at the same level of theory were then performed to identify all stationary points as minima (zero imaginary frequency) or transition states (one imaginary frequency). Calculations of intrinsic reaction coordinates (IRC)[S4] were also done on transition states to confirm that such structures are indeed connecting two minima. The effective core potentials (ECPs) of Hay and Wadt with double-ζ valence basis set (LanL2DZ)[S5] were used to describe Pd, Cl and P atoms. For all the other atoms, the standard 6-31G basis set was used.[S6] Polarization functions were added for the Pd (ζ_f(Pd) = 1.472),[S7] Cl (ζ_d(Cl) = 0.514), P (ζ_d(P) = 0.340), and the C4 and C6 atoms in 4,6-dichloro-2-pyrone (ζ_d(C) = 0.600).[S8] All calculations were performed with the use of the Gaussian 03 software package[S9] on PC Pentium IV computers.

Cartesian coordinates of all the calculated structures:

$Pd(PMe_3)_2$

E = -379.288134 a.u.

P	2.326038	0.002027	-0.002022
Pd	0.000062	-0.005954	-0.002940
P	-2.325871	0.000779	-0.002008
C	-3.186182	-0.820919	1.439825
C	-3.175845	1.665695	-0.004356
C	-3.191721	-0.829294	-1.435659
C	3.187317	-0.820133	1.438960
C	3.192814	-0.825650	-1.436492
C	3.174047	1.667947	-0.002731
H	4.266442	1.566872	0.001818
H	2.865842	2.228315	-0.891094
H	2.859168	2.231613	0.881140
H	4.283896	-0.764438	-1.340317
H	2.891963	-1.877186	-1.480629
H	2.883832	-0.343875	-2.369577
H	4.278842	-0.754150	1.349923
H	2.870214	-0.338188	2.369202
H	2.890598	-1.872874	1.482814
H	-4.277790	-0.756404	1.350710
H	-2.888132	-1.873237	1.484781
H	-2.869690	-0.337606	2.369565
H	-4.268108	1.563242	0.000382
H	-2.861614	2.230651	0.878921
H	-2.868418	2.225551	-0.893314
H	-4.282876	-0.769432	-1.339446
H	-2.883449	-0.347951	-2.369202
H	-2.889474	-1.880466	-1.478867

4,6-Dichloro-2-pyrone

E = -371.995292 a.u.

C	-2.041019	-0.534900	-1.288428
C	-1.226957	-0.231695	-0.236044
O	-1.655075	-0.065008	1.002894
C	-3.108067	-0.197522	1.376365
C	-3.951553	-0.516307	0.263294
C	-3.431081	-0.673003	-0.993327
Cl	0.482611	-0.027531	-0.415397
O	-3.366832	-0.018912	2.553576
Cl	-4.494644	-1.060232	-2.318718
H	-5.007615	-0.624915	0.466201
H	-1.655140	-0.663019	-2.287926

TS-I

E = -751.278384 a.u.

Pd	0.760193	-0.013167	0.211816
P	0.111635	2.240135	-0.321873
P	3.028724	-0.665732	-0.548018
C	3.967285	-1.699953	0.689163
C	3.078056	-1.764497	-2.056697
C	4.319771	0.606339	-0.994912
C	-1.166956	2.409382	-1.667058
C	-0.613829	3.270761	1.045623
C	1.461396	3.358157	-0.960853
H	4.935815	-2.023926	0.290765
H	4.128494	-1.117050	1.601543
H	3.371411	-2.579895	0.951114
H	4.101793	-2.079183	-2.291175
H	2.461597	-2.651460	-1.879207
H	2.660962	-1.226243	-2.913860
H	5.266831	0.128623	-1.271522
H	3.965303	1.209528	-1.836385
H	4.489311	1.270049	-0.141162
H	-1.415566	3.462008	-1.845496
H	-0.783554	1.966311	-2.591673
H	-2.073696	1.870979	-1.378916
H	1.071052	4.356390	-1.191301
H	2.249032	3.448430	-0.206120
H	1.896197	2.925932	-1.867691
H	-0.876153	4.271718	0.683643
H	-1.506637	2.775847	1.436360
H	0.116530	3.357848	1.856351
Cl	-0.018153	-1.258468	2.441453
C	-1.082748	-0.578917	0.954215
O	-1.972904	0.334053	1.363316
C	-3.378418	0.430135	0.827078
C	-3.677030	-0.533173	-0.171432
C	-2.740176	-1.491036	-0.523684
C	-1.466732	-1.599825	0.051046
O	-4.039551	1.351595	1.298254
H	-4.662539	-0.506206	-0.612753
Cl	-3.191247	-2.680992	-1.736338
H	-0.827254	-2.449173	-0.136018

TS-II

E = -751.270483 a.u.

C	1.209641	-1.723725	0.892431
C	1.067596	-1.154069	-0.384528
C	2.195947	-0.504628	-1.023860
C	3.305808	-0.320323	-0.270325
O	3.446173	-0.694227	0.995368
C	2.351378	-1.497279	1.698416

Pd	-0.820551	-0.195174	-0.230957
Cl	0.037003	-2.228853	-1.606063
Cl	4.713901	0.512863	-0.896526
O	2.628478	-1.824530	2.846537
P	-0.033658	2.051244	0.104930
C	-1.345346	3.333451	0.452801
P	-3.262507	-0.335780	0.133748
C	-4.362257	0.772028	-0.891236
C	1.086000	2.268289	1.577792
C	0.940307	2.906528	-1.237784
C	-4.002562	-2.007571	-0.241400
C	-3.936429	-0.025999	1.847369
H	-5.089036	-2.008961	-0.094383
H	-3.776899	-2.278571	-1.277614
H	-3.549660	-2.759470	0.412554
H	-5.022294	-0.173060	1.883000
H	-3.457681	-0.710508	2.554838
H	-3.704259	0.998930	2.154150
H	-5.423014	0.579094	-0.692623
H	-4.141031	1.819928	-0.664938
H	-4.158754	0.600175	-1.953094
H	1.413229	3.309676	1.677400
H	0.553643	1.968066	2.485689
H	1.964315	1.625226	1.473606
H	-0.903055	4.317597	0.647045
H	-2.018544	3.408430	-0.407413
H	-1.929181	3.026394	1.326535
H	1.218456	3.923544	-0.937448
H	1.849255	2.335321	-1.445282
H	0.339992	2.951320	-2.152086
H	0.449868	-2.375009	1.303793
H	2.142804	-0.173380	-2.050060

Complex I

E = -751.332772 a.u.

Pd	0.692779	-0.107894	-0.165882
P	0.455358	1.877216	1.060836
P	3.142337	-0.314696	-0.393868
C	3.690725	-1.950239	0.291706
C	3.686972	-0.376220	-2.166922
C	4.423263	0.827333	0.344778
C	-1.001585	2.925676	0.587127
C	0.246756	1.625246	2.883926
C	1.827232	3.129188	0.966267
H	4.749129	-2.130139	0.072584
H	3.537782	-1.962760	1.375667
H	3.073311	-2.730621	-0.158370
H	4.739482	-0.671156	-2.242228
H	3.055069	-1.099372	-2.687689
H	3.552962	0.607716	-2.628008

H	5.427706	0.440890	0.138666
H	4.338488	1.828570	-0.086778
H	4.292003	0.894869	1.429589
H	-1.017707	3.840043	1.190361
H	-0.932241	3.190972	-0.471930
H	-1.925400	2.369998	0.752501
H	1.533604	4.040860	1.498412
H	2.736439	2.732559	1.422042
H	2.033379	3.377379	-0.079336
H	0.107422	2.587329	3.389377
H	-0.626440	0.990129	3.050067
H	1.132648	1.127543	3.289947
Cl	0.727089	-2.106700	-1.500697
C	-1.323005	-0.304701	-0.034576
O	-1.816686	-0.152817	1.216346
C	-3.232632	-0.304899	1.595961
C	-4.089601	-0.630637	0.501959
C	-3.564448	-0.766742	-0.759880
C	-2.185604	-0.609901	-1.061936
O	-3.489158	-0.110719	2.785415
H	-5.143405	-0.753259	0.708339
Cl	-4.650716	-1.151681	-2.083206
H	-1.809006	-0.775622	-2.059852

Complex II

E = -751.321175 a.u.

C	-1.707929	0.865833	-1.501308
C	-1.302651	0.093047	-0.436224
C	-2.276868	-0.532657	0.413129
C	-3.592736	-0.332696	0.122458
O	-4.031299	0.411138	-0.880041
C	-3.084600	1.088036	-1.827354
Pd	0.667879	-0.247962	-0.085353
Cl	0.340615	-2.363907	-1.169123
Cl	-4.882270	-1.042257	1.063138
O	-3.613020	1.743168	-2.716585
P	0.779556	1.813309	0.997095
C	1.697860	3.115680	0.041970
P	3.022112	-0.992325	0.042122
C	4.437993	-0.026839	0.789834
C	-0.808081	2.676185	1.415676
C	1.640693	1.809247	2.645038
C	3.186992	-2.628186	0.901618
C	3.668663	-1.332721	-1.664089
H	4.194960	-3.039418	0.778470
H	2.972439	-2.507916	1.968487
H	2.447532	-3.306498	0.468720
H	4.642663	-1.832910	-1.623130
H	2.940633	-1.965913	-2.176886
H	3.767739	-0.392442	-2.216144

H	5.385560	-0.551519	0.623523
H	4.505199	0.966240	0.333306
H	4.291357	0.088467	1.868362
H	-0.602344	3.607704	1.953663
H	-1.358570	2.894006	0.497774
H	-1.428149	2.023439	2.036537
H	1.721357	4.061827	0.593933
H	2.722094	2.783329	-0.149489
H	1.199984	3.272758	-0.919579
H	1.621375	2.810706	3.088944
H	1.133551	1.109703	3.316469
H	2.678752	1.490638	2.528761
H	-1.001022	1.331668	-2.178252
H	-1.993047	-1.179980	1.230708

3.0 References

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