Cyclopalladation in pyrroles-some initiating studies

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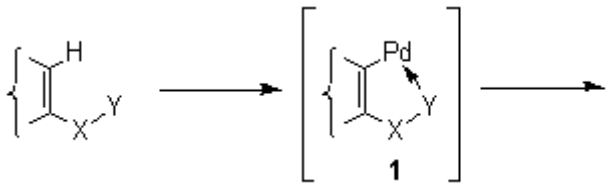
Abstract

Keywords:

Introduction

Cyclopalladation[1] of arenes implies participation by an *ortho* co-ordinating substituent such as aldehyde, ketone, amide, hydrazino, aminoalkyl, azo, imine, and iminoether, thiazole, or thioalkyl[1-4] in metallation of the arene. This process then, is a regioselective method for introduction of the metal, with replacement of hydrogen, generating intermediates which can be formulated generally as 1, and which are available for further manipulations involving use of the properties of the organometallic species.



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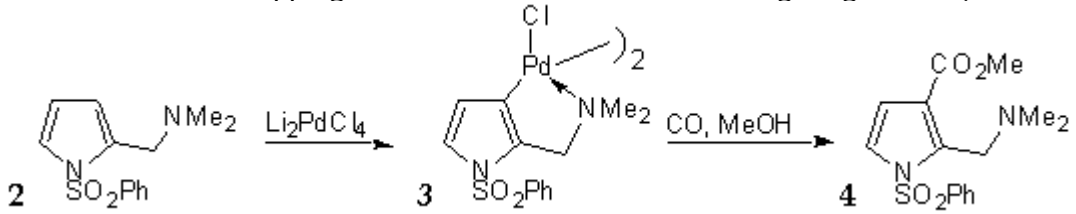
There seem to be few examples of the use of such processes in heteroaromatic chemistry: Grigg demonstrated the formation and use of complexes derived from 3-acetyl- and 4-acetylpyridines by reaction with $RuH_2CO(PPh_3)_3$, for 4- and 3-alkylations, respectively, with alkenes, and extrapolated this to the 4-alkylation of 3-benzoylpyridine and the 2-alkylation of 3-acetylindole.[5] To our knowledge, cyclopalladation has been used only once in pyrrole chemistry: 2-dimethylaminomethyl-1-phenylsulfonylpyrrole 2 reacted with lithium tetrachloropalladate(II)

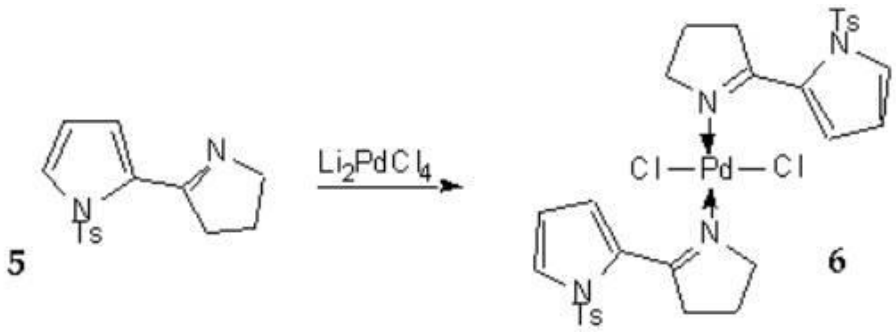
to give a solid material assigned structure 3 on the basis of spectroscopic and combustion analytical data, and of its trapping with carbon monoxide/methanol giving ester 4 (Scheme 1).[6]



Scheme 1

Result and Discussion

Arising from our interest in the synthesis of fused polycyclic molecules containing pyrrole and/or pyrrolidine rings[7] it occurred to us that the nitrogen in *cyclic* imines[8] such as 5 might also be capable of promoting cyclopalladation; there are no examples of the use of cyclic imines in such processes. Unfortunately, for our aims, reaction of 5 with lithium tetrachloropalladate(II) produced 6 (Scheme 2), as evidenced by spectroscopic data and confirmed by an X-ray crystal structure determination. Chem3D representations of the solid state structure are shown below, from perspectives chosen to show the geometry around the metal (Figure 1) and the extensively pyramidalised pyrrole nitrogen (sum of bond angles only 349.9°). We have previously commented in detail on the pyramidalisation of nitrogen in some *N*-arylsulfonylpyrroles and -indoles.[9]



Scheme 2

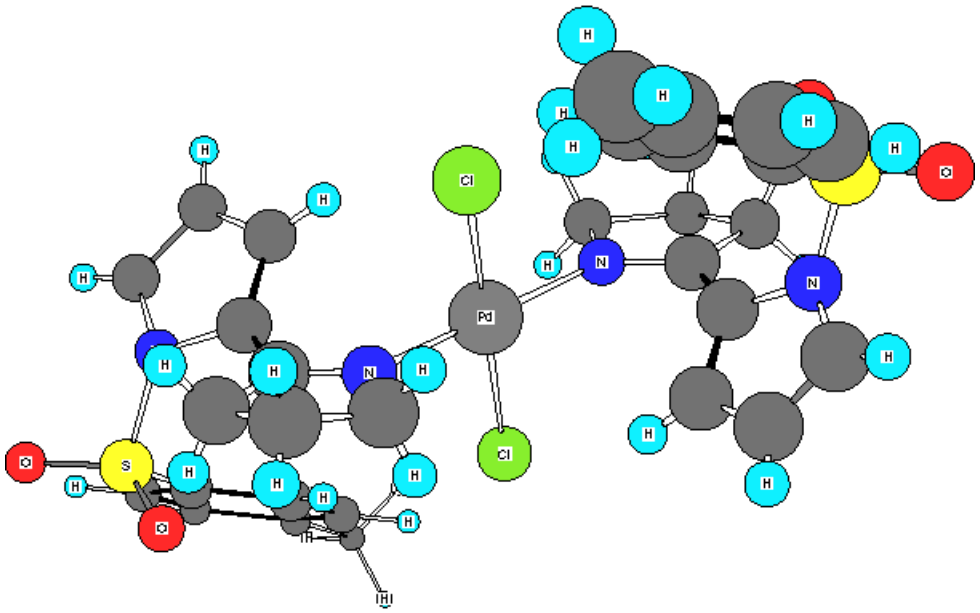


Figure 1

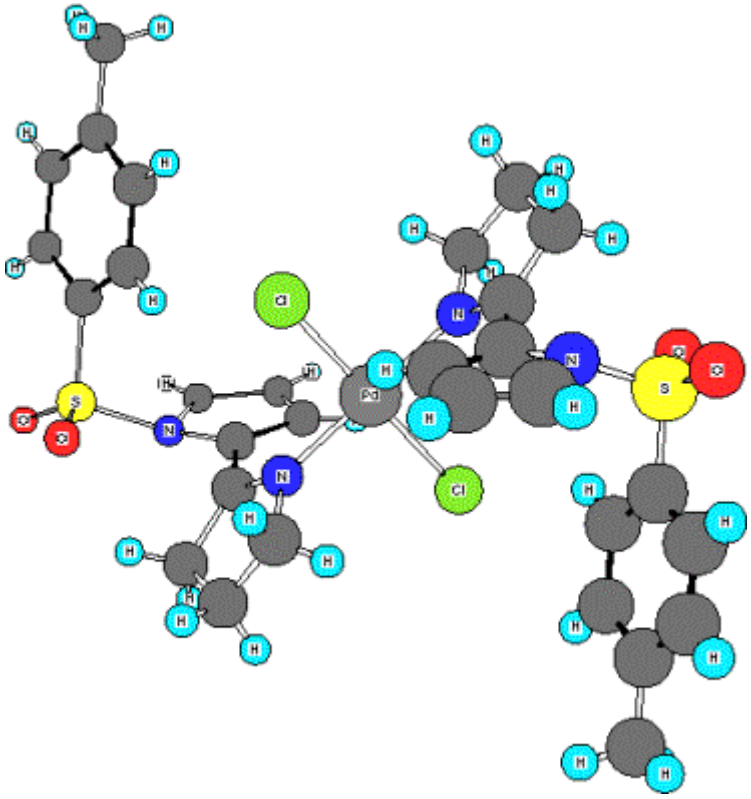
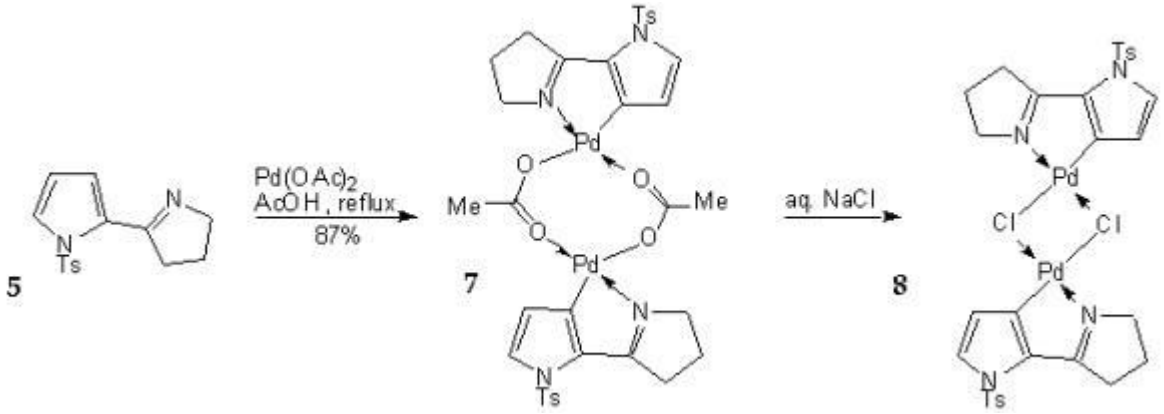


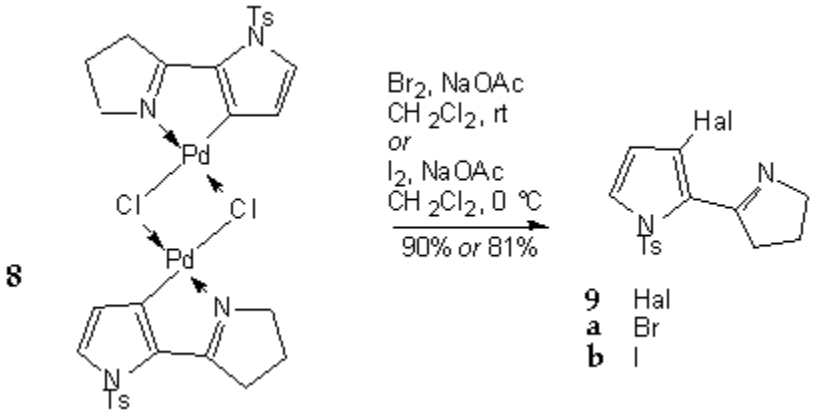
Figure 2

However, on reaction of 5 with palladium(II) acetate, the desired type of complex, 7 was obtained in good yield; treatment of 7 with sodium chloride gave the corresponding chloro-bridged complex 8 quantitatively (Scheme 3). The regiochemistry of metallation was easily confirmed by nOe experiments involving the remaining, adjacent pyrrole protons.



Scheme 3

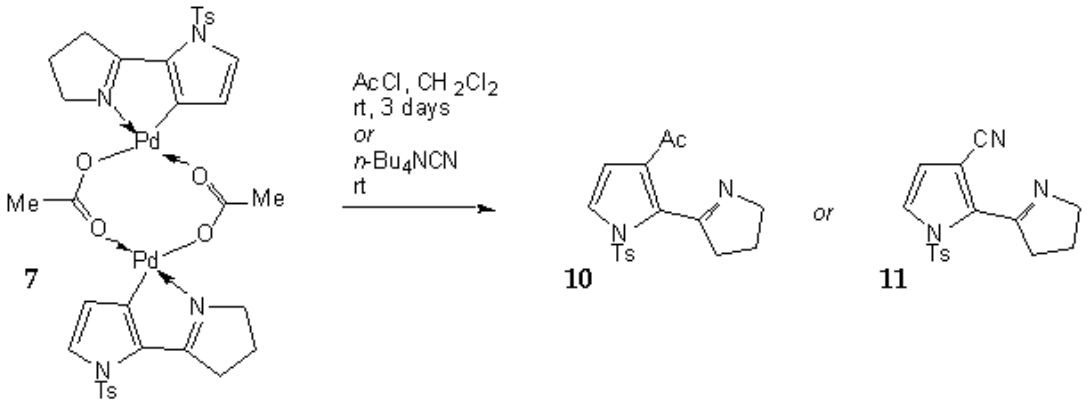
The palladium complex 8 behaved just as had been hoped in reaction with bromine and iodine, giving the 3-halogenated derivatives 9a and 9b smoothly and in high yields (Scheme 4).



Scheme 4

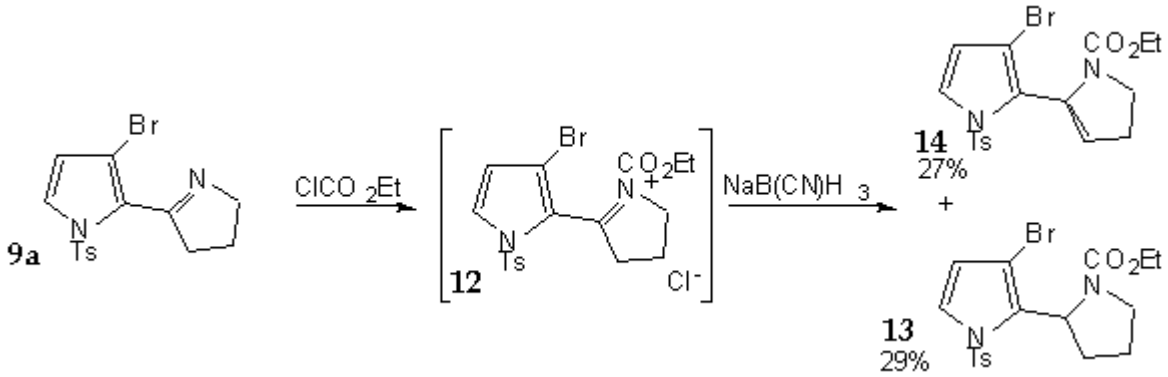
In a limited exploration of the further applicability of the cyclopalladated complex 7, it was shown that 7 could be brominated giving 9a 88% yield, acetylated in moderate yield giving 10 and that reaction with tetrabutylammonium cyanide[3] led to the formation of a cyano derivative 11 (Scheme 5) though all attempts to remove residual tetrabutylammonium residues failed (in another context we have encountered difficulties in removing residual tetrabutylammonium

fluoride from reactions involving silyl deprotection of heterocycles). No evidence for the formation of 11 was obtained on treatment of 7 with copper(I) cyanide. No useful products were obtained from 7 with cyanogen bromide, methyl vinyl ketone, styrene, benzoyl chloride, allyl bromide, ethyl chloroformate, or cyclohexyl isocyanide. Even with the limited range of successful substitutions described above, we believe that this route is capable of further development into a useful method for the preparation of 2,3-disubstituted pyrroles.



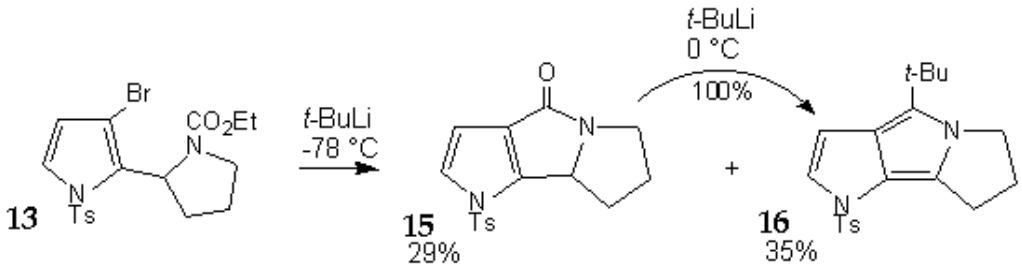
Scheme 5

Having in hand bromide 9a we examined the possibility of utilising the halogen in the formation of a third fused five-membered ring. Imine 9a was reacted with ethyl chloroformate and then, without isolation, the presumed iminium salt 12 treated with sodium cyanoborohydride. A mixture of 13 and 14 was obtained, from reduction and deprotonation, respectively (Scheme 6).



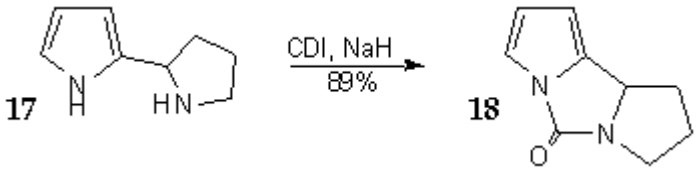
Scheme 6

Exposure of 13 to *t*-butyllithium gave the target tricyclic material 15 though only in moderate yield, accompanied by a compound molecular weight 356, into which a *t*-butyl group had been incorporated, and from which the oxygen had been lost-spectroscopic data are consistent with structure 16 (Scheme 7). In agreement with this interpretation is the finding that amide 15 was quantitatively converted into 16 on exposure to *t*-butyllithium at 0 ºC.



Scheme 7

An isomeric tricycle, urea 18, was obtained by reaction of pyrrolidine 17[10] with carbonyl diimidazole.



Experimental Section

3,4-Dihydro-5-(1-(4-methylphenylsulfonyl)pyrrol-2-yl)-2*H*-pyrrole (5). 3,4-Dihydro-5-(pyrrol-2-yl)-2*H*-pyrrole[11] (1.52 g, 0.0113 mol) was added to a suspension of NaH (0.408 g, 1.5 eq) in dry THF and the mixture stirred at rt for 30 min 4-Methylphenylsulfonyl chloride (tosyl chloride) (2.271 g, 1.5 eq) was added and the whole stirred at 0 ºC for 30 min and then at rt for 30 min. After addition of a little water, concentration and chromatography over silica (CH_2Cl_2:EtOH; 98:2) gave the *tosylamide* 5 (3.179 g, 98%) as a white solid, mp 90-91 ºC, IR (film) $_{vmax}$ 1628, 1367, 1173, 1144, 1062, 672 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm) 1.89 - 1.99 (2H, m), 2.42 (3H, s), 2.79-2.87 (2H, m), 3.94-4.02 (2H, m), 6.31 (1H, t, *J* 3.4Hz), 6.53 (1H, dd, *J* 3.4, 1.7Hz), 7.28 (2H, d, *J* 8.2Hz), 7.54 (1H, dd, *J* 3.2, 1.7Hz), 7.82 (2H, d, *J* 8.2Hz); ^{13}C NMR (100MHz, $CDCl_3$) δ (ppm) (dept) 21.623 (CH_3), 22.510 (CH_2), 38.160 (CH_2), 61.569 (CH_2), 111.308 (CH), 118.340 (CH), 126.335 (CH), 128.102 (CH), 129.149 (CH), 130.704,

136.060, 144.571, 164.923; ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm) 1.77-1.89 (2H, m), 2.41 (3H, s), 2.77 (2H, t, *J* 8.2Hz), 3.85 (2H, t, *J* 8.1Hz), 6.44 (1H, t, *J* 3.2Hz), 6.72-6.74 (1H, m), 7.43 (2H, d, *J* 8.1Hz), 7.65-7.67 (1H, m), 7.85 (2H, d, *J* 8.1Hz); ^{13}C NMR (75Mhz, DMSO-d_6) δ (ppm) 21.479, 22.345, 37.725, 61.532, 111.678, 119.368, 127.025, 128.393, 129.697, 130.401, 136.067, 145.117, 163.775; MS (EI) *m/z* 289 (MH^+, 5%), 224 (20), 223 (M^+-SO_2-H, 100), 91 (30); (CI) m/z 289 (MH^+, 100%), 135 (MH^+-Ts, 35) (HRMS Found 289.1017 and 223.1233; $C_{15}H_{17}N_2O_2S$ requires 289.1010; $C_{15}H_{15}N_2$ requires 223.1235).

Palladium complex 6. A solution of imine 5 (0.4634g, 1.609mmol) in methanol (20mL) was mixed with a solution of lithium tetrachloropalladate(II) (0.2109g, 0.5eq) in methanol (10mL) and the solution stirred at rt overnight. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (EtOH:CH_2Cl_2; 1:99), which provided the *palladium complex* 6 (0.5664g, 93%) as a yellow solid, mp 238-239ºC, IR (film) $_{vmax}$ 1623, 1374, 1175, 1129, 733, 680cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$) δ (ppm) 2.11-2.17 (2H, m), 2.25 (3H, s), 3.22 (2H, t, *J* 8.0Hz), 4.19 (2H, t, *J* 7.6Hz), 5.00 (1H, bs), 7.00 (1H, s), 7.31 (2H, d, *J* 8.0Hz), 7.42 (1H, bs), 7.93 (2H, d, *J* 8.0Hz); ^{1}H NMR (-50ºc, 300MHz $CDCl_3$) δ (ppm) 2.04-2.18 (2H, m), 2.27 (3H, s), 3.17 (2H, bs), 4.11 (2H, m), 4.61 (1H, t, *J* 3.6Hz), 6.93 (1H, dd, *J* 3, 1.2Hz), 7.21 (1H, t, *J* 1.5Hz), 7.27 (2H, d, *J* 8.4Hz), 7.87 (2H, d, *J* 8.4Hz); ^{1}H NMR (50ºC, 300MHz, $CDCl_3$) δ (ppm) 2.09 (2H, m), 2.31 (3H, s), 3.17 (2H, t, *J* 8.1Hz), 4.16 (2H, t, *J* 7.8Hz), 5.22 (1H, bs), 7.00 (1H, dd, *J* 3, 1.5Hz), 7.27 (2H, d, *J* 8.1Hz), 7.53 (1H, bs), 7.89 (2H, d, *J* 8.1Hz); ^{13}C NMR (125MHz, $CDCl^3$) δ (ppm) (dept) 21.522 (CH^3), 22.381 (CH_2), 40.522 (CH_2), 62.364 (CH_2), 114.185 (CH), 125.106 (CH), 127.925 (CH), 128.275 (CH), 129.207 (C), 129.958 (CH), 135.138 (C), 145.476 (C), 174.107 (C); NOE (-50ºC) irradiation at δ 6.93ppm gave enhancement at δ 4.61ppm (3%); irradiation at δ 4.61ppm gave enhancement at δ 6.93ppm (24%) and 7.21ppm (4%); irradiation at δ 7.21ppm gave enhancement at δ 4.61ppm (3%); no molecular ion could be detected by EI/CI, FAB, or electrospray mass spectrometry (Anal. Found: C 47.48, H 4.24, δ 7.30, Cl 10.75, S 8.29, Pd 14.09%; $C_{30}H_{32}Cl_2N_4O_4S_2Pd$ requires: C 47.79, H 4.28, δ 7.43, Cl 9.40, S 8.50, Pd 14.11%).

A crystal of approximate dimensions 0.15 x 0.04 x 0.30 mm suitable for X-ray crystallography were prepared by recrystallisation from chloroform. Data were obtained using a Rigaku AFC-5R diffractometer, graphite monochromated Cu-Ka radiation, and a rotating anode generator. Crystal data for 6; Yellow, needle crystals, triclinic, space group P1 (#2), M = 754.02; V = 788.7(2) Å^3; a = 8.2047(8), b = 12.510(1), c = 7.838(1) Å; Z = 1; D_c = 1.59g cm^{-3}; h, -7 to 10, k, -15 to 15, l, -9 to 9; R = 0.068.

Palladium complex 7. A mixture of imine 5 (1.6170g, 5.61mmol) and palladium(II) acetate (1.260g, 1eq) in acetic acid (60mL) was brought to reflux for 1 min. The resulting dark brown solution was poured into water and extracted with dichloromethane. The combined organic extracts were washed with saturated aq. $NaHCO_3$ then H_2O and dried ($MgSO_4$). Concentration and chromatography on silica (EtOH:CH_2Cl_2; 3:97) gave the *acetato-bridged complex* 7

(2.2199g, 87%) as a brown solid, mp 135-138ºC, IR (film) $_{vmax}$ 1575, 1453, 1418, 1369, 1173, 1140, 6731cm^{-1};^{1}H NMR (300MHz, $CDCl_3$) δ (ppm) 1.28-1.39 (1H, m), 1.67-1.82 (1H, m), 2.00 (3H, s), 2.35 (3H, s), 2.53 (2H, t, *J* 7.6Hz), 2.98-3.10 (1H, m), 3.34-3.48 (1H, m), 6.17 (1H, d, *J* 3.0Hz), 7.13 (1H, d, *J* 3.0Hz), 7.22 (2H, d, *J* 8.4Hz), 7.50 (2H, d, *J* 8.4Hz); NOE irradiation at d 6.17 ppm gave enhancement at δ 7.13 ppm (17%), irradiation at δ 7.13 ppm gave enhancement at δ 6.17 ppm (15%);^{13}C NMR (75MHz, $CDCl_3$) δ (ppm) (dept) 21.568 (CH_3), 21.788 (CH_2), 23.721 (CH_3), 33.176 (CH_2), 56.335 (CH_2), 116.778 (CH), 125.026 (CH), 126.402 (CH), 130.077 (CH), 130.304 (C), 135.622 (C), 145.222 (C), 146.113 (C), 173.902 (C), 181.462 (C); MS (electrospray) *m/z* 853-841 (M^+-$OCOCH_3$).

Palladium complex 8. Dissolving the acetato-bridged complex 7 in a mixture of acetone and saturated aq. sodium chloride at room temperature, then evaporation, gave *chloro-bridged complex* 8 as a yellow solid, in quantitative yield, mp >270ºC (dec.), IR (film) $_{vmax}$ 3440, 1493, 1450, 1383, 1178, 1137, 1098, 1033, 673cm^{-1}; ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm) 2.25-2.18 (4H, m), 2.45 (6H, s), 3.16 (4H, t, *J* 7.6Hz), 3.85 (4H, t, *J* 7.0Hz), 6.82 (2H, d, *J* 2.9Hz), 7.51 (4H, d, *J* 8.2Hz), 7.55 (2H, d, *J* 2.9Hz), 7.81 (4H, d, *J* 8.2Hz); NOE irradiation at δ 6.82ppm gave enhancement at δ 7.55ppm (15%), irradiation at δ 7.55ppm gave enhancement at δ 6.82ppm (24%); ^{13}C NMR (75MHz, DMSO-d_6) δ (ppm) 21.521, 22.395, 34.721, 57.949, 118.011, 126.794, 126.923, 130.871, 130.951, 135.222, 146.108, 153.840, 177.279; MS (positive electrospray, CH_3CN/H_2O carrier) *m/z* 912-899 (M^+-Cl+2´CH_3CN), 870-857 (M^+-HCl+CH_3CN), 829-816 (M^+-HCl) (Anal. %; Found: C 42.31, H 3.41, δ 6.17, Cl 8.73, S 7.65, Pd 24.79%; $C_{30}H_3Cl_2N_4O_4S_2Pd_2$ requires: C 41.98, H 3.52, δ 6.53, Cl 8.26, S 7.47, Pd 24.79).

3,4-Dihydro-5-(3-bromo-1-(4-methylphenylsulfonyl)pyrrol-2-yl)-2*H*-pyrrole (9a). A solution of bromine (0.0703g, 0.02mL, 2.2eq) and sodium acetate (0.0544g, 2eq) in CCl_4 (12mL) was added dropwise to the mixture of complex 8 (0.1716g, 0.2mmol) in CH_2Cl_2 (5mL). After the addition (30min), the original heterogeneous reaction solution had become clear and was stirred at rt for another 10 min. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aq. Na_2SO_3, NH_3-NH_4Cl aq. solution (p*H* = 10), water, and brine successively, dried ($MgSO_4$), and concentrated. Chromatography on silica (ethyl acetate:petrol ether; 3:7) afforded the *bromo compound* 9a (0.1292g, 88%) as a light brown solid, mp 94-96ºC, IR (film) $_{vmax}$ 2961, 1631, 1595, 1260, 1374, 1175, 1129, 1089, 1059, 1015, 807, 674cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm) 1.92-2.40 (2H, m), 2.32 (3H, s), 2.79-2.85 (2H, m), 3.93-4.01 (2H, m) 6.26 (1H, d, *J* 4.4Hz), 7.16 (1H, d, *J* 4.4Hz), 7.20 (2H, d, *J* 8.0Hz), 7.65 (2H, d, *J* 8.0Hz); NOE irradiation at d 7.16ppm gave enhancement at δ 6.26ppm (14.5%), irradiation at d6.26ppm gave enhancement at δ 7.16ppm (11.9%); ^{13}C NMR (100MHz, $CDCl_3$) δ (ppm) 21.485, 22.712, 39.465, 61.509, 103.311 (C-Br), 115.331, 123.077, 127.350, 127.536, 129.563, 135.194, 145.178, 167.197 (C=N); MS (EI) *m/z* 368, 366 (M^+, 6, 6%), 303 (M^+-SO_2-H, 35), 302 (45), 301 (35), 300 (46), 91 (100); (CI) *m/z* 369, 367 (MH^+, 90, 75%), 215 (MH^+-Ts+H, 100), 213 (MH^+-Ts+H, 98), 135 (22) (HRMS Found: 366.0040; $C_{15}H_{15}{}^{79}BrN_2O_2S$ requires 366.0038).

3,4-Dihydro-5-(3-iodo-1-(4-methylphenylsulfonyl)pyrrol-2-yl)-2*H*-pyrrole (9b). Iodine (0.0279g, 2.2eq) was added to a solution of complex 8 (0.0858g, 0.1mmol) and sodium acetate (0.0272g, 2eq) in dichloromethane (12mL) at 0°C. The mixture was stirred at the same temperature for 10 min. The original heterogeneous solution clarified and was diluted with CH_2Cl_2 and washed with saturated aq. Na_2SO_3, aq. NH_3-NH_4Cl (p*H* = 10), water, and brine successively, dried ($MgSO_4$), and concentrated. Chromatography on silica (ethyl acetate:petrol ether; 3:7) afforded the *iodo compound* 9b (0.0671g, 81%) as a white solid, m.p. 89-90 °C; IR (film) $_{vmax}$ 1374, 1175, 1130cm^{-1}; ^{1}H NMR (400MHz $CDCl_3$) δ (ppm) 2.04-2.12 (2H, m), 2.38 (3H, s), 2.89 (2H, tt, *J* 7.9, 2.2Hz), 4.07 (2H, tt, *J* 7.4, 2.2Hz), 6.37 (1H, d, *J* 3.2Hz), 7.19 (1H, d, *J* 3.2Hz), 7.27 (2H, d, *J* 8.5Hz), 7.71 (2H, d, *J* 8.5Hz); ^{13}C NMR (100MHz, $CDCl_3$) δ (ppm) 21.699, 23.042, 39.974, 61.768, 70.378 (C-I), 119.852, 124.032, 127.461, 129.843, 131.375, 135.282, 145.417, 168.781 (C=N); MS (EI) *m/z* 415 (MH^+, 10%), 349 (M^+-SO_2H, 40), 91 (100); (CI) m/z 415 (MH^+, 100%), 289 (MH^+-I, 10), 261 (MH^+-Ts+H, 28) (HRMS Found: 414.9971; $C_{15}H_{16}IN_2O_2S$ requires 414.9979).

3,4-Dihydro-5-(3-acetyl-1-(4-methylphenylsulfonyl)pyrrol-2-yl)-2*H*-pyrrole (10). A mixture of complex 7(0.0905g, 0.1mmol) and acetyl chloride (0.0393g, 0.036mL, 5eq) in dry dichloromethane (10mL) was stirred at rt for 3 days. The reaction mixture was diluted with CH_2Cl_2 and washed with aq. NH_3-NH_4Cl (p*H* = 10), water, and brine successively, dried ($MgSO_4$), and concentrated. Chromatography on silica (ethyl acetate:petroleum ether; 1:1) gave the *ketone* 10 (0.0322g, 49%) as a brown oil together with the original imine 5 (0.0116g, 20%). The ketone had IR (film) $_{vmax}$ 1679, 1415, 1378, 1175, 1138cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm) 2.07-2.18 (2H, m), 2.30 (3H, s), 2.39 (3H, s), 2.92 (2H, tt, *J* 8.1, 2.0Hz), 4.05 (2H, tt, *J* 7.5, 2.0Hz), 6.59 (1H, d, *J* 3.3Hz), 7.22 (2H, d, *J* 3.3Hz), 7.29 (2H, d, *J* 8.1Hz), 7.77 (2H, d, *J* 8.1Hz); NOE irradiation at δ 6.59ppm gave enhancement at δ 7.22ppm (23%), irradiation at δ 7.22ppm gave enhancement at δ 6.59ppm (20%). ^{13}C NMR (75MHz, $CDCl_3$) δ (ppm) 21.682, 23.000, 28.435, 39.944, 61.942, 112.022, 121.856, 126.620, 127.857, 129.879, 135.080, 145.820, 169.534, 193.295; MS (EI) *m/z* 331 (MH^+, 50%), 265 (M^+-SO_2H, 100), 177 (MH^+-Ts+H, 45), 175 (M^+-Ts, 38), 149 (48), 91 (75), 84 (98); (CI) *m/z* 331 (MH+, 100%), 177 (MH^+-Ts+H, 63) (HRMS Found: 265.1349 and 331.1118; $C_{17}H_{17}N_2O$ requires 265.1341; $C_{17}H_{19}N_2O_3S$ requires 331.1116).

3,4-Dihydro-5-(3-cyano-1-(4-methylphenylsulfonyl)pyrrol-2-yl)-2*H*-pyrrole (11). The complex 7 in CH_2Cl_2 was stirred with tetrabutylammonium cyanide at room temperature overnight. Dilution with CH_2Cl_2 then washing with aq. NH_3-NH_4Cl (p*H* = 10), water, and brine successively, and drying ($MgSO_4$), then concentration gave material which was partially purified by chromatography over silica (ethyl acetate/petroleum ether; 3:7) to give the *cyanide* 11 as a brown oil, ^{1}H NMR (200MHz $CDCl_3$) δ (ppm) 1.85-2.05 (2H, m), 2.30 (3H, s), 2.82 (2H, t, *J* 7.5Hz), 3.80 (2H, t, *J* 7.5Hz), 6.54 (1H, d, *J* 2.8Hz), 7.17 (2H, d, *J* 8.4Hz), 7.24 (1H, d, *J* 2.9Hz), 7.43 (2H, d, *J* 8.4Hz); MS (EI) *m/z* 223 (M^+-CN-SO_2H, 40%), 159 (M^+-Ts, 10), 142 (100); (CI)

m/z 315 (MH^+, 5%), 314 (M^+, 15), 289 (MH^+-CN, 48), 160 (MH^+-Ts, 70), 135 (MH^+-Ts-HCN, 65) (HRMS Found: 314.0968; $C_{16}H_{16}N_3O_2S$ requires 314.0963).

2-(3-Bromo-1-(4-methylphenylsulfonyl)pyrrol-2-yl)-1-ethoxycarbonylpyrrolidine 13 and 2-(3-**Bromo-1-(4-methylphenylsulfonyl)pyrrol-2-yl)-1-ethoxycarbonyl-4,5-dihydro-1*H*-pyrrole (14).** The bromide 9a (0.1627g, 0.4433mmol) was treated with ethyl chloroformate (0.064mL, 1.5eq) in dichloromethane (2mL) at -78ºC for 15min and then a solution of $NaBH_3CN$ (0.1114g, 4eq) in methanol (10mL) was added and the reaction mixture was stirred at -78 ºC for 1h and then rt for 2h. Water was added and the solvent was removed under reduced pressure. Chromatography on silica (ethyl acetate:petrol ether; 1:9) gave *bromo-urethane* 13 (0.099g, 51%) and *bromo-enamide* 14 (0.0517g, 27%), respectively. Compound 13 was a white solid, mp 98-100ºC; IR (film) ν_{max} 3392, 1698, 1417, 1375, 1185, 1174, 1116, 1089, 1025cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ (ppm) *Rotamer A*: 1.14 (3H, t, *J* 7.1Hz), 1.69-2.04 (3H, m), 2.09-2.21 (1H, m), 2.33 (3H, s), 3.34-3.60 (2H, m), 3.96 (2H, q, *J* 7.1Hz), 5.34 (1H, dd, *J* 7.4, 4.1Hz), 6.13 (1H, d, *J* 3.4Hz), 7.09 (1H, d, *J* 3.4Hz), 7.25 (2H, d, *J* 8.2Hz), 7.71 (2H, d, *J* 8.2Hz); *Rotamer B*: 0.64 (3H, t, *J* 7.0Hz),), 1.69-2.04 (3H, m), 2.09-2.21 (1H, m), 2.36 (3H, s), 3.34-3.60 (3H, m), 3.69-3.80 (1H, m), 5.13 (1H, dd, *J* 7.4, 5.2Hz), 6.17 (1H, d, *J* 3.4Hz), 7.21 (1H, d, *J* 3.6Hz), 7.25 (2H, d, *J* 8.2Hz), 7.62 (2H, d, *J* 8.2Hz); *A:B* = 1:2; MS (EI) *m/z* 442 (M^+, 3%), 440 (3), 361 (M^+-Br, 85), 287 (M^+-Ts, 25), 285 (25), 215 (M^+-Ts-COOEt+H, 23), 213 (28), 91 (100); (CI) *m/z* 443 (MH^+, 3%), 441 (3), 289 (MH^+-Ts+H, 2.3), 287 (2.8), 142 ($C_4H_6NCOOEt^+$, 100) (HRMS Found: 440.0403; $C_{18}H_{21}{}^{79}BrN_2O_4S$ requires 440.0406). Compound 14 was a yellow oil; IR (film) ν_{max} 1690, 1415, 1380, 1191, 1175, 1134cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ (ppm) 0.78-1.24 (3H, m), 2.07 (3H, s), 2.58-2.84 (2H, m), 3.58-4.10 (4H, m), 5.07 (1H, bs), 6.33 (1H, d, *J* 3.4Hz), 7.31 (2H, d, H 8.2Hz), 7.36 (1H, d, *J* 3.6Hz), 7.70 (2H, d, *J* 8.2Hz); MS (EI) *m/z* 440 (M^+, 28%), 438 (28), 359 (M^+-Br, 100), 331 (MH^+-Br-C_2H_5, 35), 295 (MH^+-Br-SO_2-H, 96), 91 (85); (CI) *m/z* 441 (MH^+, 72%), 439 (75), 287 (MH^+-Ts+H, 80), 285 (100), 174 (65), 142 (60) (HRMS Found: 438.0247; $C_{18}H_{19}{}^{79}BrN_2O_4S$ requires 438.0249).

Tricyclic lactam 15 and pyrrolo[1,2-*a*]pyrrolo[3,4-*b*]pyrrole (16). To a solution of bromo-urethane 13 (0.1130g, 0.2562mmol) in dry THF (12mL) was added *t*-BuLi (1.7M solution in pentane, 0.33mL, 2.2eq) at -78ºC. The reaction mixture was stirred at this temperature for 0.5h and then at 0ºC for 0.5h. The reaction was quenched by the addition of aq. NH_4Cl and the mixture was poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water then brine, dried ($MgSO_4$), and concentrated. Chromatography on silica (ethyl acetate:petroleum ether; 2:8 to 1:1) gave the *ketone* 15 (0.0235g, 29%) as a brown solid, mp 145-147ºC; IR (film) ν_{max} 1691, 1376, 1181, 1123cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ (ppm) 1.27-1.44 (2H, m), 2.24-2.50 (2H, m), 2.48 (3H, s), 3.31-3.38 (1H, m), 3.54-3.63 (1H, m), 4.73 (1H, dd, *J* 10.4, 5.8Hz), 6.46 (1H, d, *J* 3.3Hz), 7.15 (1H, d, *J* 3.2Hz), 7.38 (2H, d, *J* 8.2Hz), 7.80 (2H, d, *J* 8.2Hz); MS (EI) *m/z* 316 (M^+, 11%), 161 (M^+-Ts, 68), 86 (70), 84 (100); (CI) *m/z* 317 (MH^+, 100%), 163 (95) (HRMS Found: 316.0879; $C_{16}H_{16}N_2O_3S$ requires 316.0882), and

pyrrolo[1,2-*a*]pyrrolo[3,4-*b*]pyrrole 16 (0.0315g,) as an unstable brown oil, IR (film) $_{vmax}$ 1359, 1169cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm) 1.27 (9H, s), 2.28 (3H, s), 2.38-2.48 (2H, m), 3.00 (2H, t, *J* 7.0Hz), 4.03 (2H, t, *J* 7.0Hz), 6.20 (1H, d, *J* 3.7Hz), 6.79 (1H, d, *J* 3.7Hz), 7.13 (2H, d, *J* 8.0Hz), 7.60 (2H, d, *J* 8.0Hz); MS (EI) *m/z* 356 (M^+, 70%), 341 (M^+-CH_3, 75), 201 (M^+-Ts, 68), 186 (M^+-CH_3-Ts, 96), 86 (100); (CI) *m/z* 357 (MH^+, 100%).

Tricyclic urea 18. 2-(Pyrrol-2-yl)pyrrolidine[10] 17 (0.1028g, 0.7558mmol) was treated with CDI (0.1348g, 1.1eq), and NaH (0.0363g, 1.2eq) in THF and the mixture stirred at rt overnight. Chromatography on silica (ethyl acetate:petroleum ether; 1:1) gave the *urea* 18 (0.1049g, 89%) as a colourless oil, IR (film) $_{vmax}$ 1744, 1414, 1355, 1264cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm) 1.40-1.54 (1H, m), 2.10-2.37 (3H, m), 3.32-3.41 (1H, m), 3.58-3.68 (1H, m), 4.63 (1H, dd, *J* 5.5, 9.6Hz), 6.03-6.05 (1H, m), 6.35 (1H, t, *J* 3.0Hz), 6.99-7.00 (1H, m); ^{13}C NMR (75MHz, $CDCl_3$) δ (ppm) 28.287, 30.529, 43.634, 59.783, 102.401, 111.039, 115.418, 135.104, 154.50;. MS (EI) *m/z* 163 (MH^+, 50%), 162 (M^+, 100), 161 (M^+-H, 55), 134 (M^+-CO, 55), 106 (33); (CI) *m/z* 180 (MNH_4^+, 65%), 163 (MH^+, 100) (HRMS Found: 162.0797; $C_9H_{10}N_2O$ requires 162.0793).

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