

## Spirocycles via Palladium Catalysed Cascade Cyclisation-Carbonylation-Anion Capture Processes.

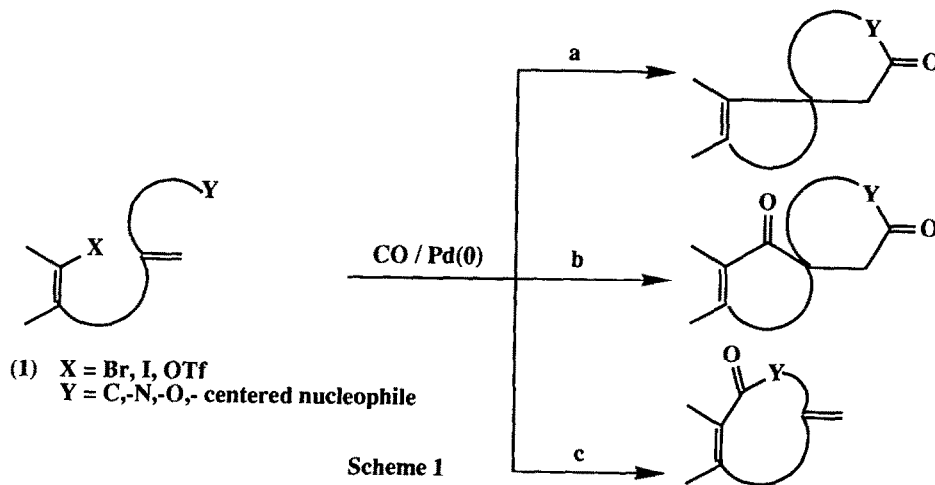
Ronald Grigg\* and Visuvanathar Sridharan

School of Chemistry, Leeds University, Leeds LS2 9JT

**Abstract.** The rate accelerating effect of thallium(I) acetate enables a palladium catalysed cascade cyclisation-carbonylation-anion capture process to occur under mild conditions [MeCN, 80°C, CO(1 atm)]. Capture of an alkylpalladium(II) intermediate by C-, O- and N- centred nucleophiles leads to spirocyclic ketones, lactones and lactams.

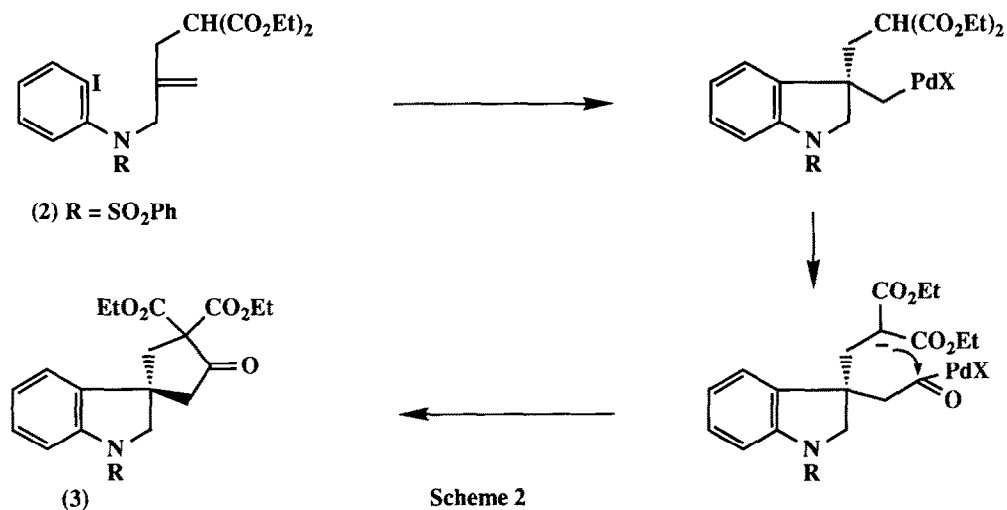
We have recently been concerned with developing palladium catalysed cyclisation-anion capture processes. This methodology has been realised for a wide range anionic (H, OAc, SO<sub>2</sub>Ph, CN),<sup>1,2</sup> neutral (CO/MeOH, amines)<sup>3</sup> and organometallic [transfer of R from B(III), Sn(IV), ZnII]<sup>4</sup> reagents. As part of a continuing investigation of these processes we recently reported cascade cyclisation-anion capture processes involving carbon monoxide insertion and subsequent methanolysis leading to incorporation of a CO<sub>2</sub>Me moiety. The rate enhancing effect of Tl(I) salts in these processes was notable and enabled the CO<sub>2</sub>Me transfers to be achieved at atmospheric pressure.<sup>5</sup>

In this communication we report palladium catalysed cascade cyclisation-carbonylation-anion capture involving intramolecular carbon-, nitrogen- and oxygen-centred nucleophiles which leads to spirocycle formation. Scheme 1 illustrates potential pathways for a substrate (1) undergoing a cyclisation-carbonylation sequence.



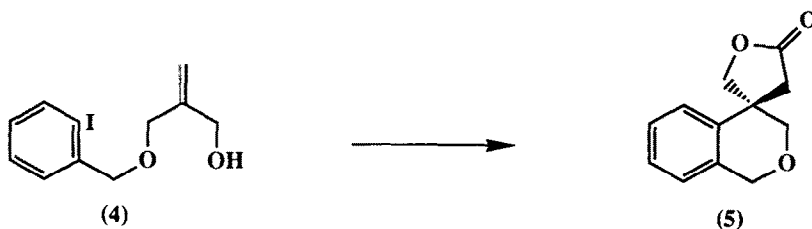
The cyclisation selectivity between paths a-c will depend on the nature of substrate which will influence the relative rates of cyclisation and carbonylation. This communication reports examples of each of these potential pathways.

The 2-iodoaniline derivative (2) undergoes palladium catalysed cyclisation-carbonylation-carbanion capture to furnish (3) (50%) when treated with a catalytic amount of palladium acetate and triphenylphosphine<sup>6</sup> in acetonitrile (80°C, 24h) under one atmosphere of carbon monoxide and in the presence of thallium(I) acetate (1.2mol) (Scheme 2).

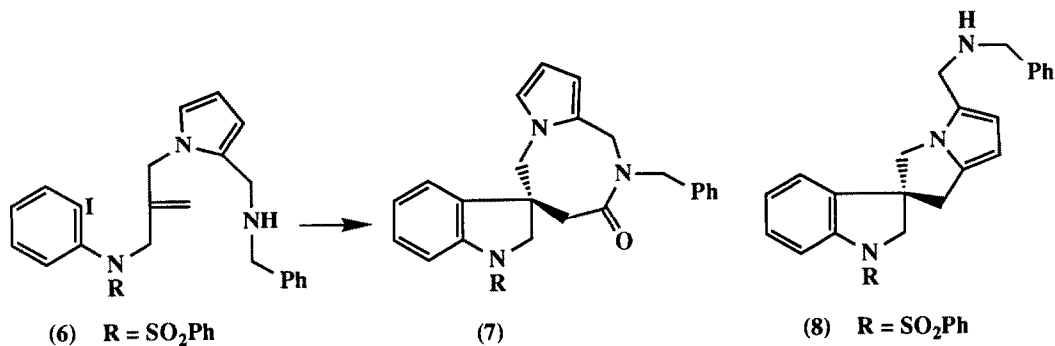


In this example (path a, Scheme 1) the 5-exo-trig cyclisation precedes carbonylation and the carbonylated intermediate is then intercepted by the proximate carbanion furnishing (3) (Scheme 2). Several related cyclisation-carbonylation processes have been reported recently but they all required temperatures  $\geq 100^\circ\text{C}$  and carbon monoxide pressures of 20-40 atmospheres.<sup>7</sup>

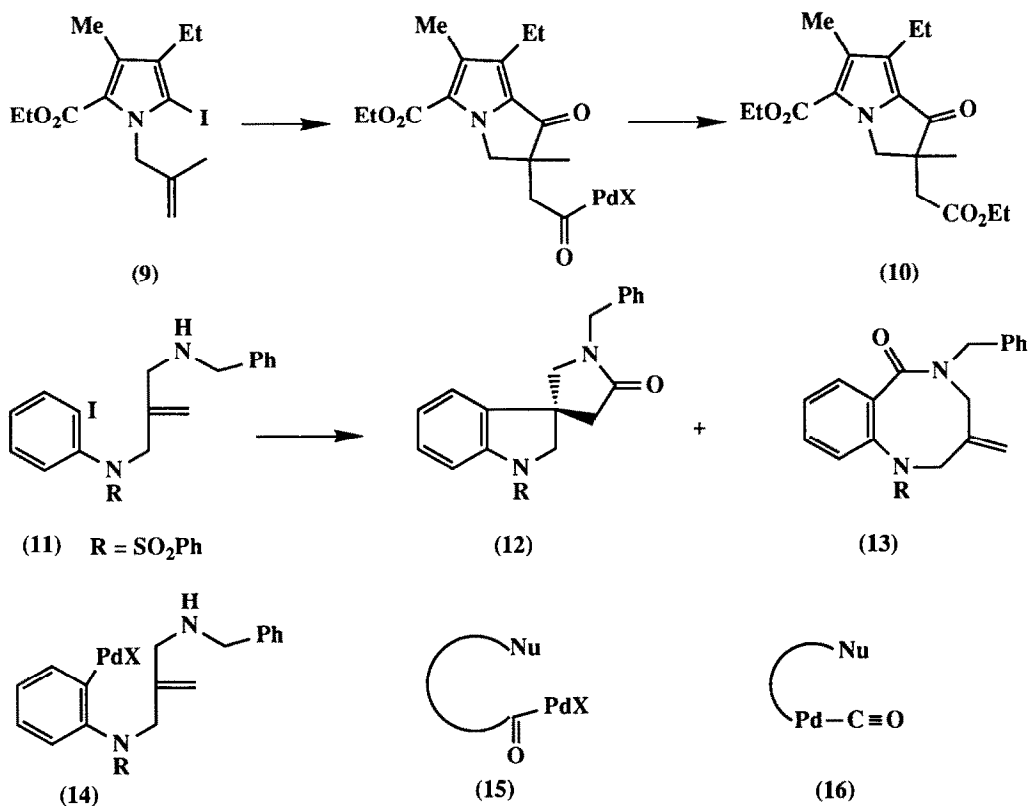
The 2-iodobenzyl ether (4) undergoes a similar cyclisation-carbonylation with interception of the carbonylated intermediate by the proximate alcohol to give the 5/6-spirocyclic lactone (5) (60%) using the same catalyst system and conditions.



Larger rings are accessible by this methodology as shown by the cyclisation (MeCN, 80°C, 2 day) of (6) to the 5/8-spirocyclic lactam (7) (45%) by the same catalyst system. None of the biscyclisation product (8) is observed in this reaction.<sup>8</sup>



A double carbonylation (path b, Scheme 1) occurs in the cyclisation (EtOH, 80°C, 24h) of (9) to (10) (50%) using our standard catalyst system<sup>6</sup> under one atmosphere of carbon monoxide. A related cyclisation-carbonylation sequence has been reported by Oppolzer.<sup>9</sup>



The iodoaniline derivative (11) undergoes cyclisation [MeCN, 80°C, CO(1 atm)] to a 1.2:1 mixture (70%) of (12) and (13) using our standard catalyst system.<sup>6</sup> Thus in this instance direct carbonylation of the arylpalladium (II) intermediate (14) competes with cyclisation. Increasing the amount of the thallium (I) acetate additive to 3mol resulted (MeCN, 60°C, 48h) in exclusive formation of the 8-membered ring product (13) (70%) via a path c process (Scheme 1).

There are two different reaction mechanisms that are possible for carbonylation reactions. One involves insertion of CO into the Pd-C bond (15) followed by nucleophilic attack, the other involves nucleophilic attack at a coordinated carbon monoxide (16) followed by reductive elimination.<sup>10</sup>

Further studies of these cascade cyclisation-carbonylation processes are under study.

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#### References.

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5. Grigg, R.; Kennewell, P., and Teasdale, A., *Tetrahedron Lett.*, 1992, **33**, 7789-7792.
6. All the reactions described in this communication employed a catalyst system comprising 10mol% Pd(OAc)<sub>2</sub> and 20mol% PPh<sub>3</sub> which generates Pd(0) *in situ*. TIOAc (1.2mol) is used in each case unless otherwise stated.
7. Wu, G.; Shimoyama, I., and Negishi, E.I., *J. Org. Chem.*, 1991, **56**, 6506-6507; Negishi, E.I.; *Pure Appl. Chem.*, 1992, **64**, 323-334; Kalinin, V.N.; Shostavsky, N.V., and Ponomaryov, A.B., *Tetrahedron Lett.*, 1992, 373-376; Tori, S.; Okumoto, H., and Xu, L.H., *ibid*, 1991, 237-240.
8. Biscyclisations of this type occur in good yield. See: Grigg, R.; Fretwell, P., Meerholtz, C., and Sridharan, V., *Tetrahedron*, in press.
9. Oppolzer, W.; Keller, T.H., Bedoya-Zurita, M., and Stone, C., *Tetrahedron Lett.*, 1989, **30**, 5883-5886.
10. Our studies do not distinguish between these two mechanistic schemes. For a fuller discussion see: Stille, J.K.; *Comprehensive Organic Synthesis*, Edit. Trost, B.M.; Fleming, I., and Semmelhack, M.E., Pergamon Press, 1991, vol.4, p 932-949.

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