PALLADIUM-CATALYSED POLYCYCLISATION-ANION CAPTURE PROCESSES

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<u>Abstract</u> Aryl iodides containing appropriately located 1, n-diene, -diyne, and -enyne moieties undergo palladium catalysed bis-cyclisation with anion capture (H^{*}, Ph^{*}) apart from the 1, n-enyne which undergoes a tri-cyclisation without anion capture. The reactions lead to the regio- and stereo-specific creation of ring junction-, spiro- and remote ring-tetrasubstituted carbon centres.

We recently developed a palladium catalysed tandem cyclisation-anion capture process whereby a vinyl- or aryl-palladium halide cyclises regio- and stereo-specifically onto a proximate alkene, alkyne or diene moiety and the resulting alkyl-, vinyl-, or π -allyl-palladium species is intercepted by an "anion" transfer agent. Typical transfer agents are formate ion (H⁻ source),¹ organo-zinc,² - tin (IV)³ and - boron² derivatives, and C-, O- and N-centred nucleophiles.⁴ Overman recently reported the first examples of palladium catalysed bis-cyclisation of 1, n-dienes in a perceptive extension of the Heck reaction⁵ and subsequently Negishi⁶ extended the process to 1, n-enynes.

We now report the results of a preliminary survey of bis-cyclisation - anion capture processes involving 1, n-dienes, -enynes and -diynes. The dienyl aryl iodide (1) undergoes a palladium catalysed⁷ cyclisation-hydride ion capture process (DMF, 80°C, 6h) to give (2a) in 70% yield using sodium formate as the hydride ion source.⁸ Dienyl aryl iodide (3) undergoes an analogous cyclisation (MeCN, 80°C, 6h)⁹ to give (4a) (70%) together with some starting material. Attempts to effect anion transfer from sodium tetraphenylborate were less rewarding in terms of yield but, significantly, the process is stereo specific. Thus (1) reacts (anisole, 80°C, 18h) in the presence of sodium tetraphenylborate (1 mol) to afford (2b) (30%), whilst (3) cyclises (anisole, 90°C, 18h)⁹ to a 2:1 mixture (70%) of (4b) and (5). Stereochemical assignments for (2b) and (4b) are based on n.O.e. data.







lodide (1) affords a 5/5 ring fusion whilst (3) gives a 6/5 ring fusion. Substrate (6) was prepared to explore both a 5/6 ring fusion and the creation of a spirocyclic system. Palladium catalysed cyclisation (DMF, 100° C, 4h) of (6) in the presence of sodium formate (1.2 mol) afforded a 2:3 mixture (50%) of (7a) and (8). Cyclisation of (6) (anisole, $110-120^{\circ}$ C, 18h) in the presence of sodium tetraphenylborate afforded (7b)(42%) as a single diastereomer together with some starting material (10%) and an as yet unidentified product (20%).

Palladium catalysed envne bis-cyclisation-anion capture was studied with (9). Cyclisation⁷ in the presence of Bu₃SnCH=CH₂ (1.2 mol) (MeCN, 25°C, 2h) or sodium formate (DMF, 70°C, 1h) did not yield anion capture products, but in both cases gave the tris-cyclisation product(10) in 40-65% yield. Evidently cyclisation of the alkyl-palladium species (11) is energetically more favourable than anion exchange and reductive-elimination.

The diyne iodide (12a) cyclises (MeCN, 70°C, 1h) in the presence of formate to give (13a) in low yield. Work up involving preparative t.l.c. resulted in some double bond isomerisation and afforded a mixture of (13a) (26%) and (14a) (6%).



Reaction of (12a) (2:1 THF-Et₂O, 25°C, 0.5h) with phenylzinc chloride (4mol)

afforded a mixture of (13b) (40%), (12b)(17%) and (14b)(26%). The structure of (14b) was established by a single crystal X-ray structure whilst the stereochemistry of (13b) (a single isomer) remains to be confirmed. A number of mechanisms can be written for the formation of (14b). One of these is shown in the scheme.

Further exemplifications and extensions of these processes, which lead to the regio- and stereospecific creation of ring junction-, spiro- and remote ring-tetrasubstituted carbon centres, are under study.

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<u>References</u>

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- All reactions employed 10 mol % Pd(OAc)₂, 20 mol % PPh₃, and 1 mol. Et₄NCl unless otherwise noted. The use of tetraalkylammonium halides to promote Heck type reactions was introduced by Jeffrey, see e.g. Jeffery, T., Synthesis, 1987, 70-71 and earlier papers.
- Yields refer to isolated material. All new compounds gave satisfactory analytical and spectroscopic data.
- Reaction carried out as in reference 7 but with AgNO₃ (1 mol) replacing Et₄NCI. The use of silver salts to promote Heck reactions was introduced by Hallberg, see e.g. Karabelas, K.; Hallberg, A., *J. Org. Chem.*, 1986, <u>51</u>, 5286-5290; see also reference 5.

<u>Illustrative procedure</u>: A mixture of enamide (1) (680 mg), $Pd(OAc)_2$ (44mg), $PPh_3(104mg)$, $Et_4NCI(320 mg)$ and $HCO_2Na(168 mg)$ in dry DMF (20 ml) was stirred and heated at 80°C under an atmosphere of dry nitrogen for 6 h. The cooled reaction mixture was then filtered, the solvent removed under reduced pressure and the residue partitioned between ether (100 ml) and water (50 ml). The ether layer was dried and evaporated to leave an oil which was purified by preparative to t.l.c.(silica) eluting with 2:3 v/v ether-petroleum ether to afford(2a) (290 mg, 70%) as a colourless oil (Found: C, 78.25; H, 8.2; N, 6.6. $C_{14}H_{17}NO$ requires C, 78.1; H, 7.95; N, 6.5%); $\delta(CDCI_3)$ 7.8-7.4(m, 4H, ArH), 3.89 and 3.10(2 x d, 2 x 1H, J 11.9 Hz, NCH₂), 1.80(2 x d, 2 H, CH₂), 1.53 (s, 3H, NCMe), and 1.23 and 0.83(2 x s, 2 x 3H, Me); m/z(%) 215(M⁺, 55), 200(34), 159(100) and 130(26).

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