Palladium Catalysed Intermolecular Cascade Cyclisation - Cyclopropanation Reactions.

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Abstract. Catalytic four -step cascade cyclopropanations involving an intermolecular olefin insertion step are readly achieved. The processes may be terminated by β - hydride elimination or hydride ion capture and provide flexible new methodology for multiple C-C bond formation.

We recently reported a series of facile bis - cyclisation processes proceeding via alkylpalladium(II) intermediates and resulting in the formation of tricyclic systems containing 3- and 4-membered rings in excellent yield. These processes, of which $(1)\rightarrow(3)$ (70-80%) is a typical example, were all intramolecular cascades.¹ Subsequently Negishi² and de Meijere³ have published further examples of such processes.



The synthetic potential of cascade processes generating strained ring systems would be greatly enhanced if such processes were to incorporate intermolecular step(s). We now report examples of such processes. The alkynyl aryl iodide (4), on heating with norbornene in boiling acetonitrile in the presence of 10 mol% palladium acetate, 20 mol% triphenylphosphine⁴ and triethylamine (2mol) afforded a single cyclopropanated norbornene stereoisomer (40%) formulated as (6) on spectroscopic and mechanistic considerations. Thus in the 300MHz p.m.r. spectrum (CDCl₃) of (6) H_A appears an unresolved triplet supporting a trans arrangement of H_A and H_B.⁵



Scheme



(7)

(5b)

The signal for H_B occurs as a doublet (3Hz) at δ 0.91 suggesting that the H_B protons have endo – stereochemistry⁵ which accords with the expected exo – face attack on norbornene. The intermediate alkylpalladium(II) species (5) can conceptually undergo cyclisation – cyclopropanation via two pre - transition state π - complexes (5a) and (5b). Cyclisation of (5a) leads, after β – hydride elimination, to the observed product (6) whilst (5b), which would lead to (7), experiences unsupportable steric interactions between the alkene substituent and the syn – proton of the norbornane C(7) - methylene group in (5b), and analogous interactions are present in (7). The cascade cyclisation– cyclopropanation outlined in the scheme is initiated by a 6 - exo - dig cyclisation which is followed by an intermolecular addition to norbornene and then a second cyclisation (3 - exo - trig). Some preliminary variations of initial cyclisation ring size and subsitution have been explored.



The alkynyl iodide (8a) cyclises under analogous conditions to those used for (4) to give (9a) in 45% yield. Cyclisation of (8b) to (9b) (40%) occurs at room temperature over 18h using the same catalyst system but with potassium carbonate (2mol) as base and in the presence of tetraethylammonium chloride (1mol) .^{6,7} In this case the p.m.r. signal for H_A occurs at δ 1.88(t, J 2.6 Hz) whilst the H_B protons give rise to a doublet (J 2.6 Hz) at δ 1.09. Alkyne (8c) cyclises to (9c) (45%) under the same conditions used for cyclisation of (4). The stereochemistry of (9c) is assigned on the basis of positive n.O.e.'s between the H_B protons (δ 1.0) and the indole proton H_C (δ 6.6, 4.8%) and the aryl proton H_D (δ 7.7, 1.2%). Thus, geminally disubstituted cyclopropanes can be prepared by this methodology.

We have previously observed the palladium catalysed cyclisation - hydride ion capture (10) \rightarrow (12) (DMF, 80°C) in 74% yield using a modified catalyst system⁸. It was of interest to use (10) to explore the effect of Ag(I) and Tl(I) salts as additives on the relative rates⁷ of 3 - exo - trig cyclisation (11) \rightarrow (13) \rightarrow (14) and direct hydride ion capture (11) \rightarrow (12) by the alkylpalladium (II) intermediate (11)

Reaction of (10) (80° C,16 h) with the previously used catalyst system,⁸ but with acetonitrile as solvent and replacing the tetraethylammonium chloride by one mole of silver (AgClO₄, Ag₃PO₄, AgOTf) or thallium (TIOAc) salt, produced a ca. 2:1 mixture of (12) and (14) in each case. Efforts to improve the selectivity for (14) are continuing.

In summary, intermolecular components can be introduced into the cascade cyclisation - cyclopropanation methodology and geminally substituted cyclopropanes can be created in this way. Preliminary results suggest it will be possible to link the cascade process to our novel palladium catalysed cyclisation - anion capture methodology.^{7,8}

Further studies of these and related processes are underway.

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Reference

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- 4. All the reactions reported in this paper employed 10 mol% palladium acetate and 20 mol% triphenylphosphine and were carried out in acetonitrile.
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- Burns, B.; Grigg, R.; Sridharan, V.; Santhakumar, V.; Stevenson, P.; Worakun, T. *Tetrahedron*, in press. The catalyst system comprised 10mol% Pd(OAc)₂, 20mol% PPh₃, Et₄N⁺Cl⁻ (1mol) and sodium formate (1.1 mol) as the hydride ion source.