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Palladium Catalysed Cascade Hydrostannylation-Bis-Cyclisation-Intramolecular Anion Capture. Routes to Bridged- and Spiro-Cyclic Small and Macrocyclic Heterocycles.

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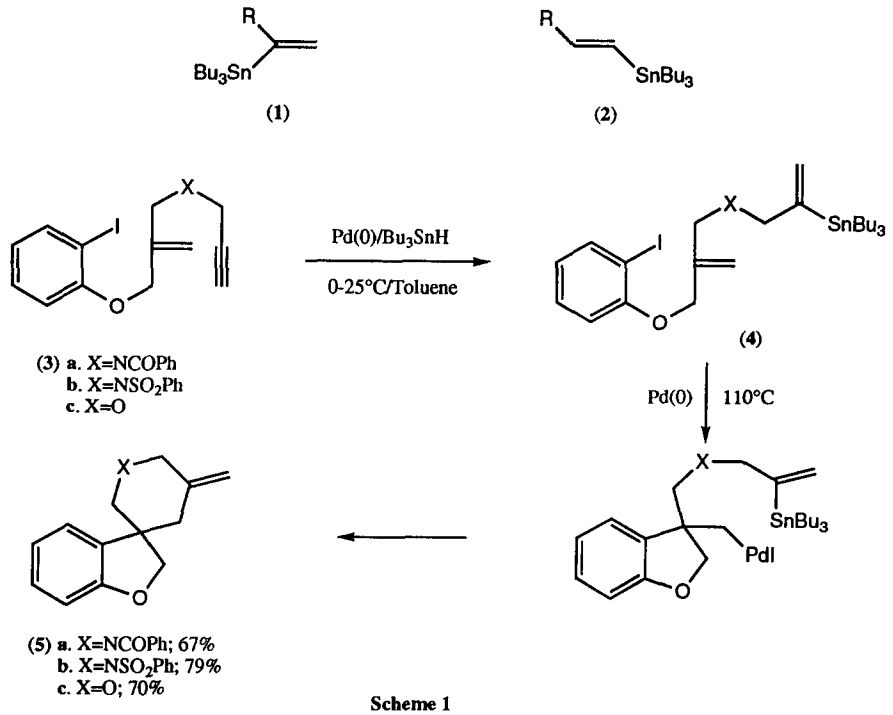
Abstract: Palladium catalysed cascade hydrostannylation of terminal alkynes in α,ω-enynes at 0-25°C followed by bis-cyclisation initiated by insertion of Pd(0) into an aryl iodide at 100-110°C and terminating in an intramolecular Stille coupling provides a wide range of exo-methylene 5/6 and 5/12-17 membered spiro- and bridged-ring heterocycles. Copyright © 1996 Elsevier Science Ltd

A growing number of imaginative applications of the intramolecular Stille reaction for the construction of macrocyclic natural products have been reported following the pioneering work of Stille, Hegedus and Hirama.[1-3] These applications have mainly employed sp^2-sp^2 Stille coupling apart from Hirama's and Danishefsky's (sp-sp^2) work.[2,3] Macrocycle formation via sp^2-sp^3 Stille coupling has not been reported. We have shown that organotin(IV) reagents are excellent anion capture agents in our intermolecular palladium catalysed cascade cyclisation-anion capture processes[4] and that anion capture is invariably slower than cyclisation when 3-7 membered rings are being constructed. Moreover, these cascade processes offer the opportunity to explore **sp^2-sp^3 Stille coupling as part of a polycyclisation strategy which incorporates a macrocyclisation**. The successful implementation of such processes via palladium catalysed cascade cyclisation-intramolecular anion capture is reported herein.

The ready Pd(0) catalysed hydrostannylation of alkynes offered the possibility of a Pd(0) catalysed cascade process in which cyclisation-anion capture occurs intramolecularly. Good to excellent regioselective hydrostannylation of terminal alkynes can be achieved by the incorporation of a proximate (β- or γ-) heteroatom[5]. Bis-cyclisation processes involving creation of two small rings were explored as a prelude to macrocyclisation studies. In developing a cascade cyclisation-intramolecular anion capture process for small ring polycycles it is essential to generate the α-vinylstannane (1) since the β-vinylstannane (2) presents a sterically impossible barrier to anion capture.

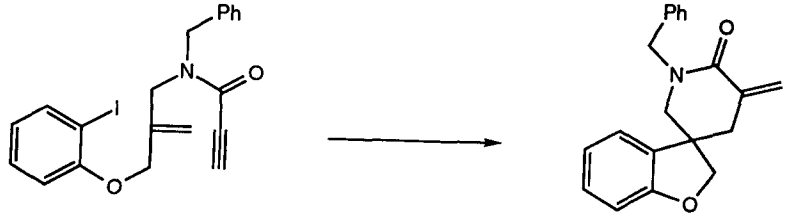
A series of eneynes (3a-c) (Scheme 1) was allowed to react with Bu_3SnH(1eq) in toluene at 0-25°C over 1h in the presence of 10mol% $Pd(OAc)_2$ and 20mol% PPh_3 at which time hydrostannylation was judged complete by ^1H n.m.r. monitoring. In the case of (3a) and (3b) only the α-vinylstannanes (4a) and (4b) were detected whilst (3c) gave a 3:1 mixture of (4c) and another stannane presumed to be the (E)-β-vinylstannane.

Heating the reaction mixtures to 100°C induced cyclisation-intramolecular anion capture furnishing (5a), (5b) and (5c) in 67, 79 and 70% overall yield respectively from (3a-c) based on α-vinylstannane (Scheme 1).



Scheme 1

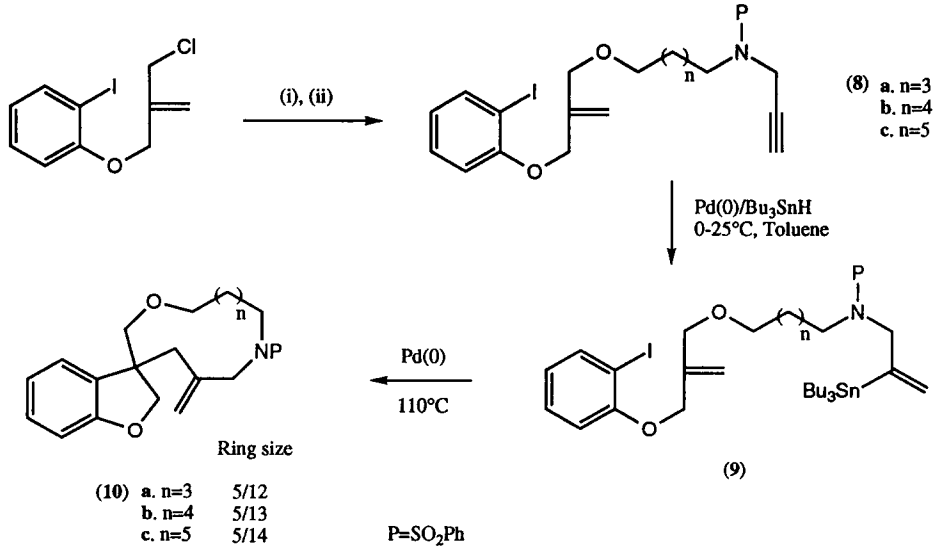
An analogous cascade, using the same conditions and catalyst system, was carried out on (6) which afforded (7) in 56% yield.



(6) (7)

The foregoing results encouraged us to explore macrocyclisation cascades. A series of enynes (8a-c) was prepared as outlined in Scheme 2. Hydrostannylation of (8a-c) (0.05 molar solutions) was carried out as described previously and gave the α-vinylstannanes (9a-c) as the only detectable (^{1}H n.m.r.) products. Heating the diluted reaction mixture ($5x10^{-3}$ molar solutions) at 100°C (toluene) gave the macrocyclic spirocycles (10a-c) in 59, 44 and 53% overall yields from (8a-c) respectively (Scheme 2). The yield of (10c) was raised from 28% to 59% by syringe pump addition of the solution of (9c) to a solution of an additional charge of catalyst [10mol% $Pd(OAc)_2$, 20mol%PPh_3] in toluene at 100°C over 20h.

A second series of macrocyclic spirocycles (12) has been prepared from (11). In this case the preferred catalyst comprised 5mol% Pd_2 (dba)$_3$ and 20mol% tri(2-furyl)phosphine. Hydrostannylation at 0°C was less selective than previously and afforded 2:1 mixtures of the α- and β-vinylstannanes. Bis-cyclisation proceeded smoothly at 100°C ($5x10^{-3}$ molar solutions) over 12h to afford (12) in 50-53% yield (Table 1).



Scheme 2. (i) HO$\overset{}{\frown}_n$OH , NaH, DMF, 0°C. (ii)HC≡CCH$_2$NHSO$_2$Ph, ADDP, PBu$_3$, Toluene, 25°C

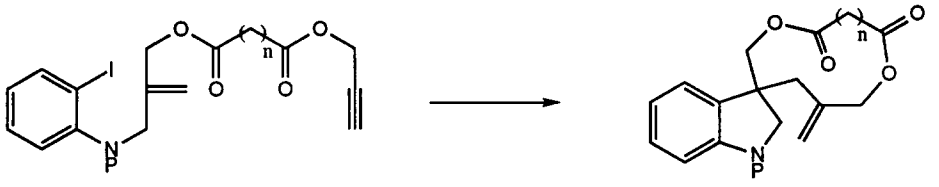
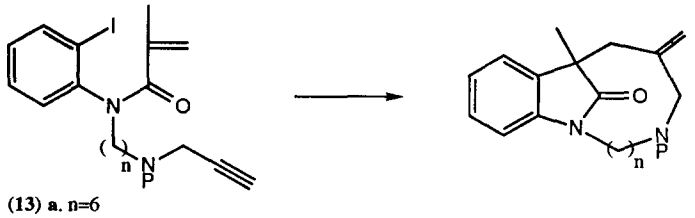


Table 1. Biscyclisation-intramolecular anion capture of (11) to (12).

n	macrocyclic ring	Yield(5)[a]
3	12	53 (71)
4	13	52 (70)
5	14	52 (70)
6	15	53 (71)
7	16	50 (67)
8	17	53 (71)

a. Isolated yields. Yields in brackets are corrected for the α-/β-vinylstanne ratio.

A series of bridged-ring forming macrocyclisations employing (13a-c) afforded the desired products (14a-c) in moderate yield. In these cases the preferred catalyst system comprised 10mol% $Pd_2(dba)_3$, 80mol% tri(2-furyl)phosphine and LiCl(1-3eq). The bis-cyclisations employed $5x10^{-3}$ molar solutions and were complete in 2-4h at 110°C. Monitoring the hydrostannylation reactions (0.05 molar solutions) by ^1H n.m.r. indicated only the desired α-vinylstannane was being formed.



(13) a. n=6
b. n=7
c. n=8

P=SO_2Ph

	Ring size	Yield (%)
(14) a. n=6	13	51
b. n=7	14	24
c. n=8	15	36

The reactions described in this paper demonstrate the synthetic potential of hydrostannylation-polycyclisation-intramolecular anion capture cascades and research is continuing on these and related processes.

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