Pergamon

Tetrahedron Letters 39 (1998) 489–492

TETRAHEDRON LETTERS

On the *Cine* Substitution of 1,1-Bis(Tri-n-Butylstannyl)ethenes in an Intramolecular Stille Reaction

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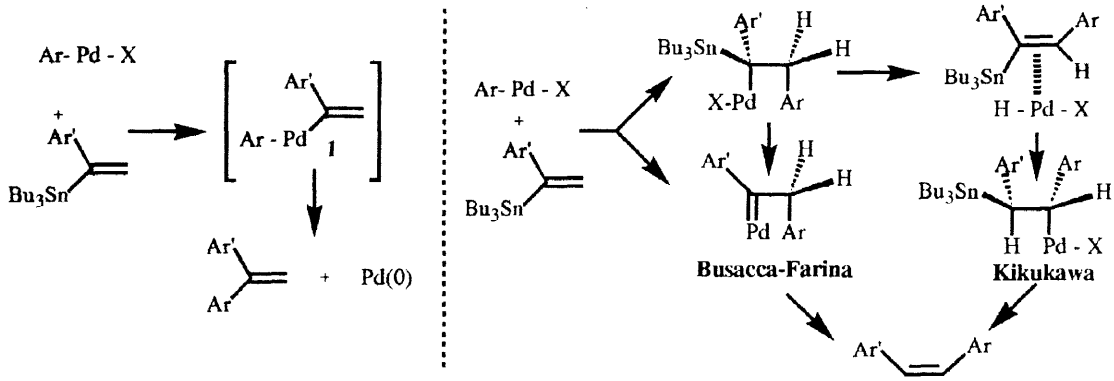
Received 6 October 1997; revised 27 October 1997; accepted 7 November 1997

Abstract: An attempted intramolecular Stille coupling of a *bis*-stannylethene proceeds not by *ipso*-substitution (7-*endo*-cyclisation) but *via* a *cine* substitution pathway (6-*exo*-cyclisation). Deuterium labelling studies and blank reactions are in consonance with a palladium carbene mechanism originally put forward by Busacca to explain the *cine* substitution reactions of styrylstannanes.

The Stille reaction is now a well established procedure for the synthesis of olefins, polyenes and polyunsaturated systems.[1] This is especially true when coupling reactions between two functionalised components in a stereodefined manner are required. The currently accepted[2] mechanism of the Stille reaction, as outlined below, relies upon the stereospecific transmetallation reaction between a vinyl- or arylstannane and an alkyl- or aryl palladium (II) species to form the intermediate **1**. Reductive elimination results in carbon-carbon bond formation and the liberated Pd(0) is then able to re-enter into the catalytic cycle, **Scheme 1**.



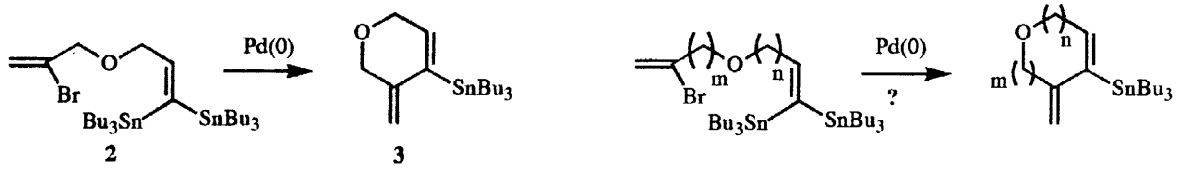
Stille reaction — **Scheme 1** — Cine-substitution

Occasionally, as in the case of the intermolecular coupling reactions of α-styryl tin derivatives, products of *cine* substitution are observed.[3] The mechanism of this reaction has been the subject of some debate, although the intermediacy of palladium carbene complexes (Busacca-Farina pathway) now appears likely,[4,5]

0040-4039/98/$19.00
PII: S0040-4039(97)10584-6

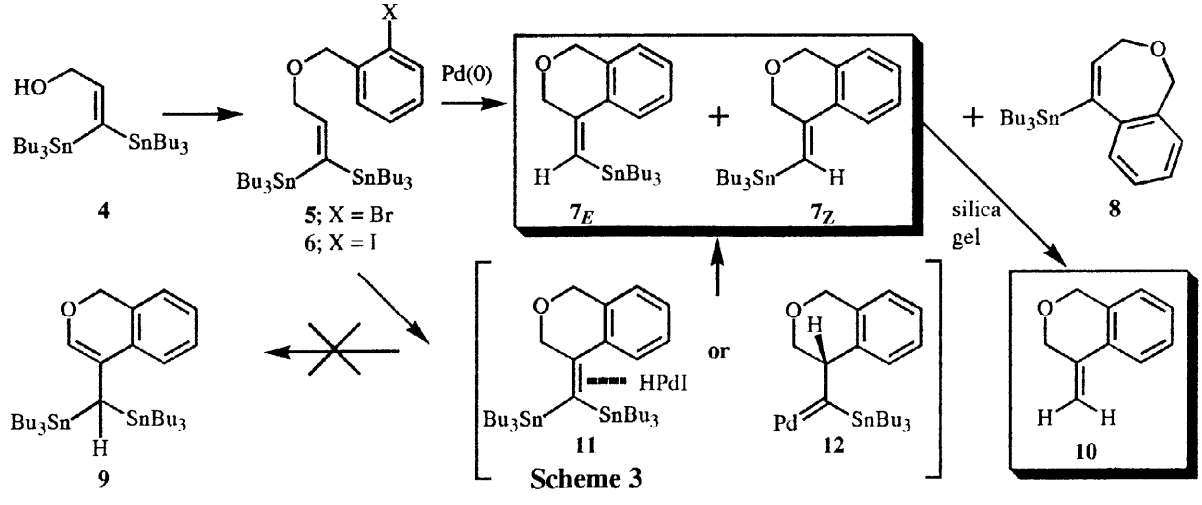
Scheme 1. Steric[3a,b] and, more recently, electronic factors[6] have been held responsible for this switch in mechanism.

In a continuation of our studies into the chemistry of 1,1-*bis*(tri-n-butylstannyl)ethenes[7] we reported that the bromide **2** underwent clean intramolecular coupling[8] affording the diene **3** in 54% isolated yield. To examine the generality of these intramolecular Stille coupling reactions we extended our studies to the synthesis of medium ring heterocycles, **Scheme 2**. The synthesis of seven membered ring heterocycles *via* the Stille reaction has little precedent[9]: only one example of an oxepin synthesis has been reported.[10] This strategy would enable rapid construction of key structural features present in a number of biologically important natural products.



Scheme 2

The vinylstannanes **5** and **6** were readily prepared[11] by alkylation of the alcohol **4** with either o-bromobenzylbromide (NaH, 1.2 eq.; imidazole, 1.2 eq.; DMF; 20 °C;) or o-iodobenzylbromide. Initial attempts to perform the intramolecular Stille reaction on the bromide **5** were problematical. After some experimentation, we were able to effect cyclisation albeit in low yield (*ca.* 20% yield) using Pd(0) generated *in situ* ($Pd(OAc)_2$, 10 mol%; $P(o\text{-}Tol)_3$; Et_3N, 3% *v/v*; CH_3CN; 80 °C). Examination of the ^{1}Hnmr spectrum of this crude reaction mixture suggested that the major cyclisation pathway led to the formation of a mixture of the isomeric vinylstannanes 7_E and 7_Z. Oxepin **8** [^{1}Hnmr δ 4.04 ppm (d, J = 5.5 Hz); 6.27 ppm (t, J = 5.5 Hz)] was present in trace quantities (<5%) whereas the vinyl ether **9** could not be detected. Column chromatography of this reaction mixture afforded a low yield (20%) of the exocyclic alkene **10** as the only identifiable product.

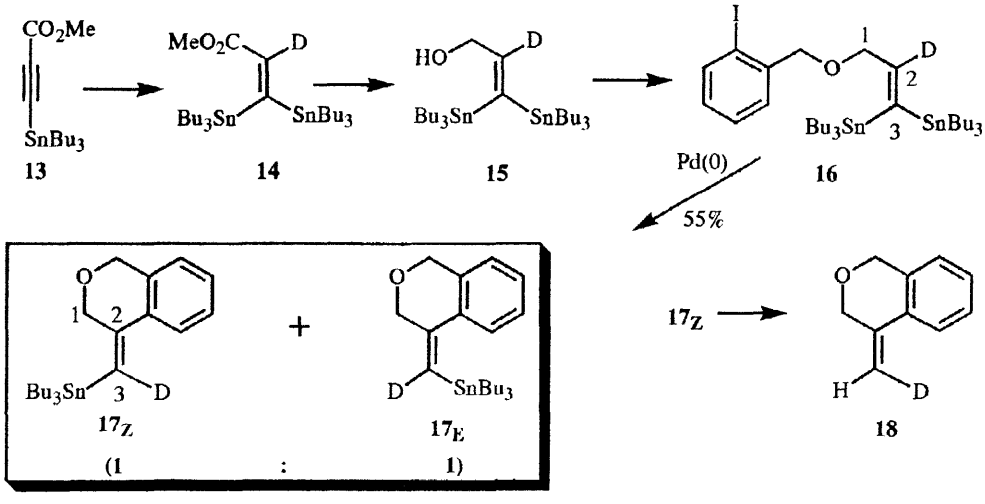


Scheme 3

A more satisfactory outcome was achieved using the iodide **6**. The ^{1}Hnmr spectrum of the crude reaction mixture indicated that cyclisation had again proceeded in a 6-*exo*-fashion, affording a 1:1 mixture of the vinyl

stannanes, 7_E and 7_Z, along with *ca.* 20% unreacted starting material **6**. Chromatography of this reaction mixture, on base-treated silica gel, resulted in selective protodestannylation of 7_E and afforded a mixture of the exocyclic alkene **10** and stannane 7_Z (7_Z:**10** = 1.5:1) in 54% yield. Neither formation of the oxepin **8** or the isomerised alkene **9** could be detected. The formation of **7** could in principle be accommodated by two limiting mechanisms: that involving the formation and re-addition of a hydridopalladium species to the alkene **11** or *via* the intermediacy of a palladium carbene complex **12**, **Scheme 3**.

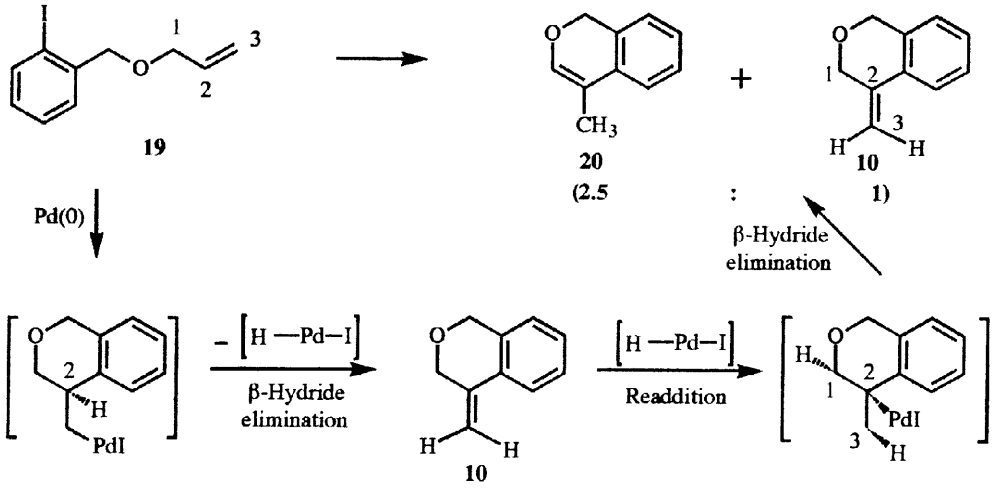
We reasoned that incorporation of a deuterium label into **6**, as in **15**, would allow us rationalize our experimental results. In turn **15** would be readily accessible using our recently developed methodology for the synthesis of bis-stannylethenes.[12] Treatment of acetylene **13** with neat tri-n-butyltin deuteride (1.2 eq., >95% D, Aldrich; AIBN, cat.; 90 °C; 4 hrs.) afforded stannane **14** in 46% yield. Reduction of ester **14** with Dibal-H (2.4 eq., THF; 0 °C; 4 hrs.) and chromatography led to the isolation of the alcohol **15** in 64% yield with >95% D incorporation at C_2. Conversion of **15** to the ether **16** was uneventful (2-iodobenzylbromide, 2 eq.; NaH, 2 eq.; DMF; 20 °C; 94%) and proceeded without diminution of the deuterium label. The crucial palladium catalysed reaction was performed under the same experimental conditions as for **5** and **6** and proceeded cleanly to an ***E/Z*** mixture of the vinyl stannanes **17**. On this occasion chromatography was accomplished without loss of the tin moiety and afforded an isomeric mixture (***E*:Z** = 1:1) of the vinyl stannanes **17** in 55% yield, together with recovered starting material **16** (5% isolated yield). Exposure of the geometrically pure stannane 17_Z to camphorsulfonic acid (2 eq.; CH_2Cl_2; 20 °C; 1 hr.) afforded the alkene **18** as the sole organic product in 88% yield. Comparison of the ^{1}Hnmr spectrum of **18** with the ^{1}Hnmr spectrum of the crude reaction mixture of the palladium reaction confirmed that none of this product had not formed during the cyclisation reaction, **Scheme 4**.



Scheme 4

The fact that cyclisation of **16** proceeded without scrambling of the deuterium label or double bond migration, is inconsistent with the hydridopalladium readdition process as proposed by Kikukawa[3a] and is more readily accommodated by invoking the Busacca-Farina palladium carbene mechanism, **Scheme 3**.[5,6] In order to test this hypothesis the related alkene **19** was subjected to standard Heck conditions, which are believed to

generate hydridopalladium intermediates.[1] Double bond migration was observed in this case, affording a mixture of the 6-*exo* cyclisation products **10** and **20** (**20:10** = 2.5:1). This result *is consistent* with the formation of hydridopalladium intermediates which add reversibly to the initial cyclisation product **10**, leading ultimately to double bond isomerisation forming **20**, with proton scrambling between C_1, C_2 and C_3, **Scheme 5**.



Scheme 5

In conclusion, 6-*exo*-cyclisation of the substrates **5**, **6**, **16** and **19** is more favoured than 7-*endo* cyclisation, presumably due to steric and stereoelectronic effects. In the case of **16** lack of deuterium scrambling provides additional circumstantial evidence for the intermediacy of palladium carbene complexes in *cine* substitution reactions of vinylstannanes in Stille coupling reactions.

ACKNOWLEDGEMENTS

J. W. and J. X. thank the CVCP for provision of ORS Awards and the University of Manchester for Postgraduate Research Scholarships. In addition we thank Zeneca for generous support of this work.

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