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Stereoselective Stille Coupling Reactions of 1,1-Bis(Trialkylstannyl)ethenes

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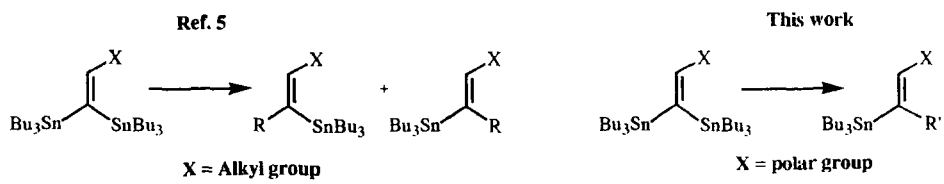
Abstract: Stille coupling of 1,1-*bis*(tri-n-butylstannyl)ethenes proceeds in a stereoselective manner to afford the *E*-vinylstannanes. Repetition of this sequence affords a new route to tri-substituted alkenes. Intramolecular Stille coupling of a suitable vinyl bromide affords a pyranyl-derived vinylstannane. In certain cases, with bulky electrophiles, butyl migration rather than that of the sp^2- hybridised centre is observed. A working model is put forward in order to rationalise these results.

The palladium catalysed cross-coupling reaction of organometallic reagents with vinyl or aromatic (heteroaromatic) halides is a well established process. In particular, the coupling reactions between stereodefined vinylstannanes (or boronic acids) with unsaturated halides and pseudohalides - the Stille[1] (or Suzuki[2]) reaction - provides direct access to highly unsaturated systems with a high degree of stereochemical control. Apart from the desirable stereochemical features of these reactions, their functional group tolerance, generality, unsophisticated experimental procedures and ease of execution, all serve to promote their use in multistep syntheses, a situation which has been exploited extensively in recent years.[3]

In contrast the cross coupling of bi-metallic reagents in such reactions has enjoyed scant attention being limited primarily to the use of 1,2-*bis*(tributylstannyl)ethenes[4a] and 1,2-*bis*(tributylstannyl)ethyne.[4b] The use of 1,1- *bis*(tributylstannyl)ethenes in such coupling processes has been briefly mentioned,[5] and in the case cited, was shown to be non-selective, affording a mixture of mono- and difunctionalised olefins, **Scheme 1**.



Scheme 1

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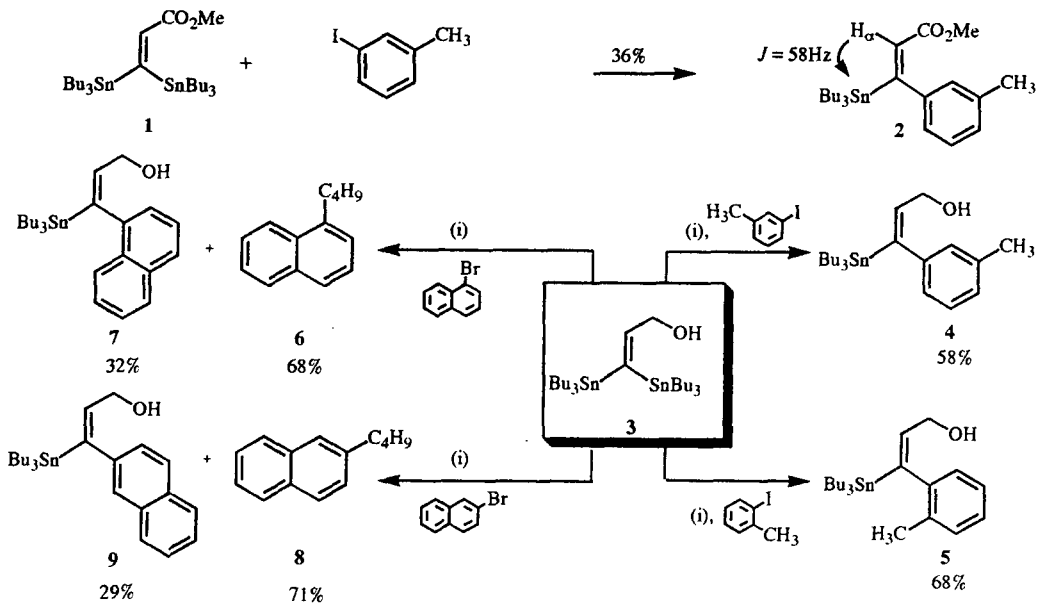
Continuing our studies of 1,1-*bis*(tributylstannyl)ethenes[6] we questioned whether such substrates could undergo stereoselective C-C bond formation reactions in a sequential manner and thereby provide access to tri-substituted alkenes,[7] which can be difficult to prepare in a stereoselective sense using existing methodology. Treatment of the ester **1** with *m*-iodotoluene, in the presence of palladium acetate and tri-*o*-tolylphosphine ($Pd(OAc)_2$, 10 mol%; P(*o*-Tol)$_3$, 20 mol%) in refluxing acetonitrile containing triethylamine (3 %v/v) for 20 hours, resulted in the isolation of the coupled[8] product **2** in moderate yield 36%, together with recovered starting material **1** (22% yield). It is noteworthy that, although sluggish, the reaction afforded the coupled product solely as the *E* -isomer **2**. This stereochemical assignment was made upon the basis[9] of the small ^3J coupling constant between Sn and H_α (58 Hz). It has been noted by other workers[10] that electron withdrawing substituents on the vinylstannane moiety can retard the rate of the Stille reaction, an effect which we could readily evaluate by conversion of the ester **1** to the alcohol **3**.[6a] In this instance, coupling of the alcohol **3** with either *m*- or *o*-iodotoluene afforded the coupled products **4** and **5** with much greater levels of efficiency (58% and 68% respectively) under the same standard reaction conditions, **Scheme 2**.

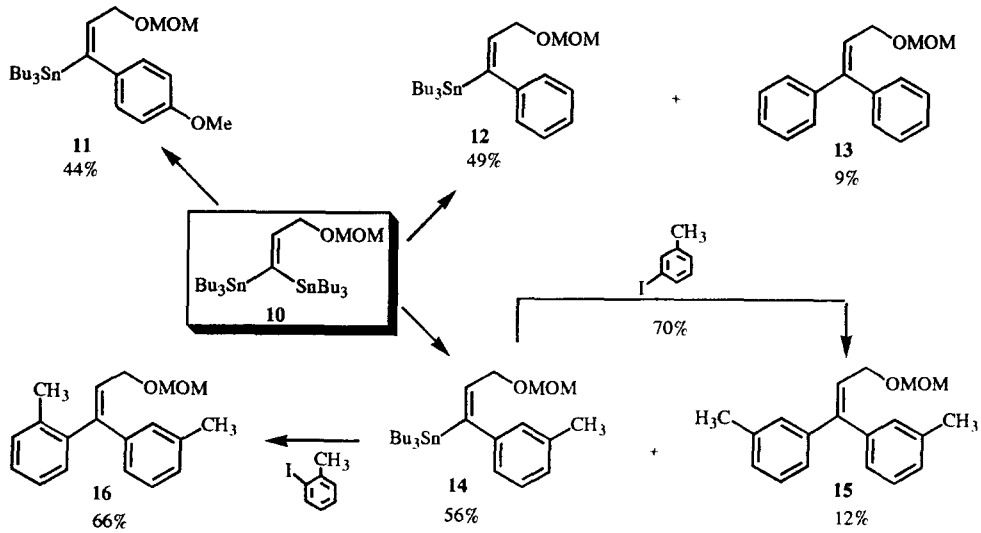


Standard reaction conditions: (i)ArX, 1.2 eq.; $Pd(OAc)_2$, 10 mol%; P(*o*-Tol)$_3$, 20 mol%; CH_3CN; 80 °C; 20 hrs.

Scheme 2

It should again be noted that both coupling reactions afforded the *E*-isomers **4** and **5** as the sole products together with minor amounts of starting material **1**. Changes in the starting palladium catalyst [*e.g.* use of $PdCl_2(CH_3CN)_2$], ligand [$AsPh_3$[11] rather than P(*o*-Tol)$_3$] or the inclusion of other additives such as copper(I) salts[12] failed to make any significant improvement in either the overall rate or yield of these coupling reactions. In fact, in the latter case, addition of catalytic quantities of copper(I) had a deleterious effect on the yield of the reaction (yield dropped to 29%). When more bulky aromatic electrophiles, such as 1- and 2-bromonaphthalene, were used, a competing coupling pathway was observed, leading to the isolation of 1-butylnaphthalene **6** and 2-

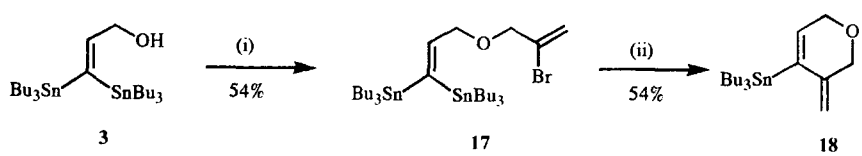
butylnaphthalene **8** in 68% and 71% yield respectively. In these examples the "normal" coupled products **7** and **9** were also isolated in 32% and 29% respectively, **Scheme 2**. Coupling of the readily available MOM-ether **10**[6a] with a variety of aryl iodides was also briefly examined. Treatment of **10** with aryl iodides again afforded the mono-coupled *E*-vinylstannanes **11**, **12** and **14** as the major products, along with minor amounts of *bis*-coupled products **13** and **15**. Although we have not yet optimised these coupling reactions, this basic methodology provides access to tri-substituted olefins *via* sequential cross coupling reactions. For example, treatment of the vinylstannane **14** with *m*-iodotoluene, under our standard reaction conditions, afforded the tri-substituted olefin **15** in 70% yield, whereas, reaction of **14** with *o*-iodotoulene afforded the unsymmetrically coupled product **16** in 66% isolated yield, **Scheme 3**.



Standard reaction conditions: ArX, 1.2 eq.; $Pd(OAc)_2$, 10 mol%; P(*o*-Tol)$_3$, 20 mol%; CH_3CN; 80 °C; 20 hrs.

Scheme 3

The use of intramolecular[13] Stille coupling reactions of geminal *bis*-stannanes would, as applied to small-medium ring synthesis, necessarily proceed in a stereoselective manner. In an initial exploration of the intramolecular Stille reaction on these substrates we have found that the readily available vinylbromide **17** underwent clean cyclisation to the vinylstannane **18** in 54% yield, **Scheme 4**.

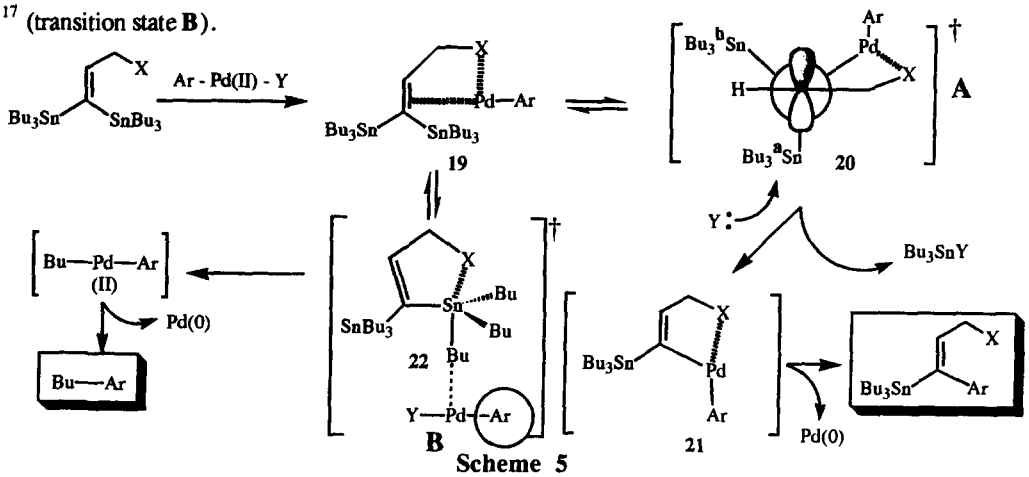


Reagents and conditions: (i) NaH, 2 eq.; 2,3-dibromopropene, 1.2 eq.; DMF; 0 °C; (ii) $Pd(OAc)_2$, 10mol%; P(*o*-Tol)$_3$, 20 mol%; CH_3CN, 80 °C; 20 hrs.

Scheme 4

Several observations in this preliminary study deserve comment, the most noteworthy being the stereochemical outcome of these reactions. Our *working* model for these reactions invokes the formation of an intermediate π-complex **19** prior to transmetallation.[14] Rearrangement of **19** *via* the chelated[15] intermediate **20** affords the vinyl palladium(II) intermediate **21**. Reductive elimination generates the observed product with concomitant formation of Pd(0) which can then re-enter into the catalytic cycle, **Scheme 5**. Preferential loss of

tin moiety *a* from **20**, *via* an antiperiplanar transition state, determines the stereochemical course of the transmetallation reaction and hence of the overall coupling sequence. When the organic electrophile is not too bulky transition state **A** is preferred leading to transfer of the vinyl group of the stannane to palladium. In the case of more sterically demanding electrophiles such as 1-bromonaphthalene, it is not unreasonable to suggest that reaction of the aryl-Pd(II) intermediate proceeds *via* an open S_E2 mechanism, in which transfer of a butyl rather than a vinyl group is now observed.[16] This may, in part, be assisted by interaction of the proximal polar group **X** with the tin moiety, facilitating transfer of the axial butyl group from the pentaco-ordinate intermediate **22**,[17] (transition state **B**).



Scheme 5

We are currently investigating these mechanistic points and synthetic applications of this alkene synthesis.

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