

On the Mechanism of Cine Substitution in the Stille Reaction: New Evidence for the Intermediacy of Pd(0) Carbenes

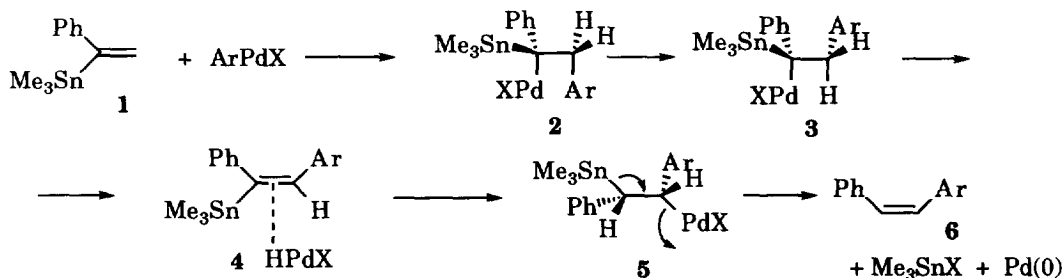
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Abstract: A dihydronaphthalene stannane was found to couple with aryl iodides to give exclusively cine substitution instead of the expected Stille product. A crossover study ruled out a mechanism previously proposed that included a disfavored *anti* beta-elimination of Pd-H, and provides further evidence for the involvement of Pd(0) carbenes in these processes. Copyright © 1996 Elsevier Science Ltd

The Stille reaction has emerged in recent years as a powerful method for the stereospecific and chemoselective formation of carbon-carbon bonds.¹ One of the limitations that has recently surfaced consists in the tendency of certain α -substituted olefinic stannanes to undergo cine substitution. This was first reported in 1986 by Kikukawa *et al.*,² who obtained (*Z*)-stilbenes **6** upon attempted Stille coupling of α -styryltins **1** with a number of aryl diazonium salts (Scheme 1). As a rationale for this unexpected result, the authors invoke, in the first step, a carbopalladation as observed in the Heck reaction. This would be followed by rotation to **3**, where the *syn* orientation needed for a β -elimination of Pd-H is achieved. Readdition of HPdX across the double bond with opposite regiochemistry, followed by an *anti* elimination of tin halide and Pd(0), would then yield the observed product and regenerate the catalyst. Evidently, the expected Stille-type transmetalation is disfavored on steric grounds.

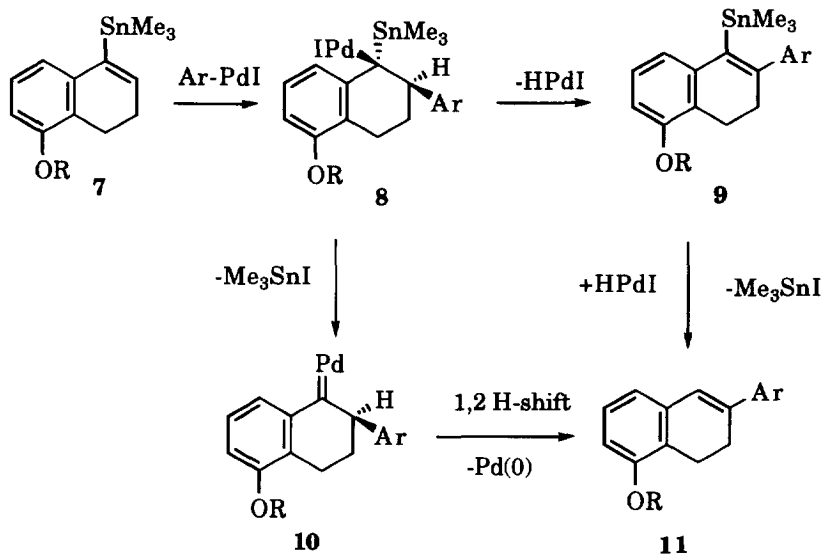
Scheme 1



After this initial report, other authors have observed the same phenomenon.³ The above mechanism is not unreasonable, but contains a number of undocumented steps, and the absence of the uncomplexed stannane **4** among the reaction products is puzzling. More recently, Busacca *et al.* have proposed a convincing alternative to the Kikukawa mechanism: these authors invoked the intermediacy of a Pd(0) carbene complex that would form from **3** via α -elimination of Me₃SnX.⁴ Their evidence rests mainly on the net retention of deuterium in the 1- \rightarrow 2 hydrogen migration. However, in *acyclic* stannane **1**, *syn* elimination of Pd-H, formation of π complex **4**, and *syn* readdition can also easily explain the net label retention. The Kikukawa mechanism, therefore, cannot be ruled out based on D retention, and a more definitive experiment must be carried out.

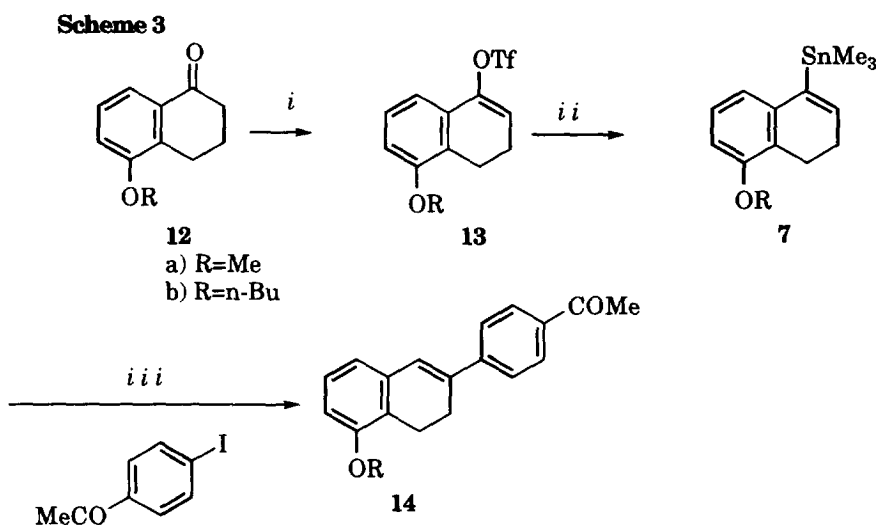
We decided to modify the Kikukawa substrate into a *cyclic* system, *e.g.* **7** (Scheme 2). Carbopalladation of this substrate would yield **8**. The Kikukawa mechanism would now require an *anti* β -elimination of Pd-H, a theoretically disfavored pathway, which has nonetheless been invoked previously.^{3a} The *anti* relationship between Pd and the hydrogen atom would dictate that the "HPdI" species become initially dissociated from the stannane double bond, and requires that, in a crossover experiment, crossover products be observed. The Busacca mechanism, on the other hand, involves an intramolecular 1,2 hydrogen shift (**10** \rightarrow **11**), and predicts no crossover products. We now report a study that clearly confirms Busacca's mechanism and disproves the mechanism of Scheme 1, at least for cyclic stannanes. It also provides an alternative rationale for the observation of apparent (and disfavored) thermal *anti* β -Pd-H elimination reported by some authors.^{3a}

Scheme 2



Our chemistry is shown in Scheme 3. Triflates **13a,b**, prepared by a known method,⁵ were successfully subjected to reaction with hexamethylditin, using the Wulff procedure.⁶

The required stannanes **7** were treated with *p*-iodoacetophenone under our standard cross-coupling conditions.⁷ As predicted, only the cine substitution products (**14a,b**) were obtained. Of the solvents studied, the reaction was cleanest in toluene and, even though rather drastic conditions were required in this solvent, we decided to employ it for our crossover study. In addition, this solvent has been used in previous cine substitution experiments,^{3a} and we thought its use would make our study more compelling. For the crossover study, stannane **7a** was labeled at the β position with deuterium by subjecting **12a** to standard H/D exchange (MeONa/MeOD, rt, 16h), followed by triflation and stannation as before, to yield **7c** (>98% D, Scheme 4).

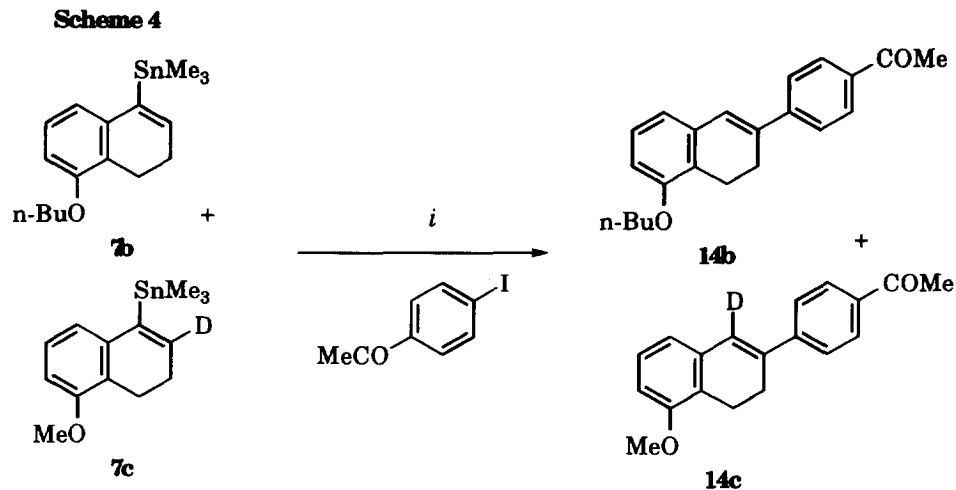


Conditions: (i) Tf₂O, 2,6-di-*t*-Bu-4-Me-pyridine, ClCH₂CH₂Cl, rt (82% for **13a**, 86% for **13b**); (ii) Me₃SnSnMe₃, Pd(PPh₃)₄, LiCl, THF, 60° (64% for **7a**, 79% for **7b**); (iii) Pd₂(dba)₃, AsPh₃, PhMe, 110° (48% for **14a**, 50% for **14b**).

The results of the crossover experiment are shown in Scheme 4: when an equimolar mixture of **7b** and **7c** was subjected to coupling under the previously discussed conditions with a slight excess of *p*-iodoacetophenone, only the "intramolecular" products **14b** and **14c** were observed. In particular, no loss of deuterium (<5%) in **14c** and no D incorporation (<2%) in **14b** were detected.

This result strongly supports the involvement of Pd(0) carbenes in the cine Stille coupling and disproves the occurrence of the "thermal" *anti* β -elimination of Pd-H,⁸ a pathway that has been proposed from time to time in the literature, but whose occurrence has never been conclusively demonstrated.

Several other studies have proposed the intermediacy of Pd(0) carbenes.^{9,10} These studies have provided some evidence for Pd(0) carbenes through a variety of trapping experiments and have hinted at their synthetic utility. Efforts at further characterizing these Pd(0) carbenes and expanding their utility in organic synthesis are now under way and will be disclosed in due course.¹¹



Conditions: (i) $\text{Pd}_2(\text{dba})_3$, AsPh_3 , PhMe , 110° (29% for **14b**, 26% for **14c**).

References and Notes

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- All new compounds were characterized by ^1H and ^{13}C NMR and mass spectroscopy, as well as elemental analysis (C,H).

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