

Communication

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## Cine-Substitution in the Stille Coupling: Evidence for the Carbenoid Reactivity of $sp^3$ -gem-Organodimetallic Iodopalladio-trialkylstannylalkane Intermediates

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Palladium-catalyzed cross-coupling reactions are general and commonly used synthetic methods for the formation of carbon–carbon bonds.<sup>2</sup> The cross-coupling methodologies tolerate a wide array of functional groups and display high regioselectivity and stereospecificity. When vinylmetals are used as coupling partners, however, a reversal of regioselectivity and formation of the *cine*-substitution products is often observed. The *cine*-substitution is most frequently encountered in the Stille coupling of  $\alpha$ -substituted vinyl stannanes,<sup>3</sup> and methods overcoming this selectivity problem have been reported.<sup>4</sup>

Two widely accepted *cine*-substitution mechanisms have been postulated: the Kikukawa<sup>3g</sup> and the Busacca–Farina<sup>3d,e</sup> mechanisms. The initial formation of a key  $sp^3$ -gem-dimetallic Pd-stannylalkane intermediate **2**, via regioselective migratory insertion of PhPd(II)X (X = I, BF<sub>4</sub>) into the vinylstannane **1**, is suggested for both mechanistic pathways (Scheme 1).

Kikukawa proposed that intermediate **2** undergoes a  $\beta$ -hydride elimination to afford the vinylstannane **3**.<sup>3g</sup> Subsequent hydro-palladation across the alkene with opposite regiochemistry followed by anti elimination of Bu<sub>3</sub>SnBF<sub>4</sub> and regeneration of the catalyst leads to the *cine*-product **4**. All efforts to detect and identify the uncomplexed vinylstannane **3** have been unsuccessful.

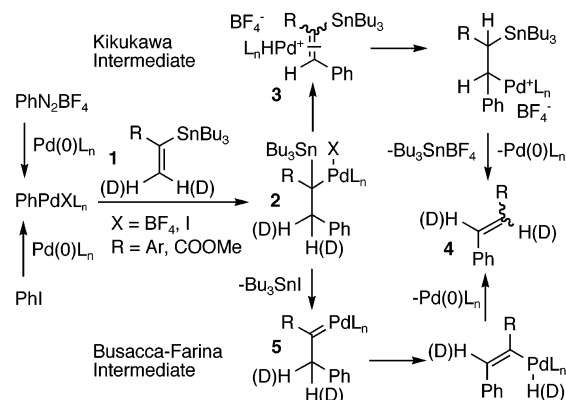
Labeling and crossover experiments by Busacca and Farina<sup>3d,e</sup> provided evidence to support a mechanism involving an intermediate palladium-carbene **5**, formed via a four-center transmetalation of the *gem*-dimetallic intermediate **2** with loss of Bu<sub>3</sub>SnI (Scheme 1). A 1,3-hydride shift followed by reductive elimination afforded the *cine*-substitution product **4**.

The synthetic importance of the Stille coupling demands that the *cine*-substitution mechanism be clearly established.

Providing that the  $\beta$ -hydride shift is not an available reaction pathway, the preparation of the  $sp^3$ -gem-dimetallic halo-Pd(II)/trialkylstannylalkane species should lead to Pd-stabilized carbenes following the Busacca–Farina mechanism, and further react in reactions typical of metal-carbenes.<sup>5</sup> This Communication reports two approaches for the preparation of *gem*-dimetallic iodopalladio-trialkylstannylalkane complexes as Pd-carbenoid precursors to probe the *cine*-substitution mechanism in the Stille coupling.

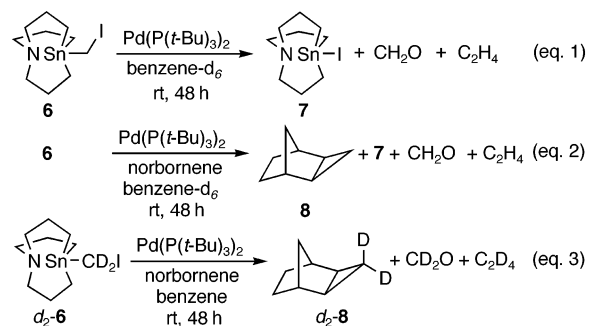
Our initial efforts were directed at generating  $sp^3$ -gem-dimetallic iodo-Pd/trialkylstannylalkane species by oxidative insertion of Pd(0) catalysts into iodomethyltrialkylstannanes. It was anticipated that the decomposition of iodomethyltrialkylstannanes by Pd(0) catalysts would lead to the formation of ethylene by dimerization of the carbenoid intermediate. To test this hypothesis, iodomethylstannane (**6**) ( $\delta_H = 1.68$ ,  $\delta_{Sn} = -29.1$ ) was decomposed in benzene-*d*<sub>6</sub> in the presence of Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub> (25 mol %) at room temperature for 36–48 h.<sup>7</sup> The reactions were carried out in sealed NMR tubes and monitored by <sup>1</sup>H and <sup>119</sup>Sn NMR spectroscopy.<sup>8</sup> Most rewarding, the presence of ethylene ( $\delta_H = 5.24$ ) (not quantified) and iodostannane (**7**) ( $\delta_{Sn} = -57.8$ ) was detected, with competitive

Scheme 1



formation of formaldehyde ( $\delta_H = 8.75$ ) (<1%) (eq 1).<sup>9</sup> More importantly, when the decomposition of **6** was carried out in the presence of a 5-fold excess of norbornene, *exo*-tricyclo[3.2.1.0<sup>2,4</sup>]-octane (**8**) was formed in 64% yield (eq 2).<sup>10</sup> Ethylene and CH<sub>2</sub>O were also present.<sup>11</sup> These observations were consistent with the intermediacy of a methylene carbenoid species.

Iodomethylstannane (**6**) displayed an enhanced reactivity in the oxidative insertion reaction as compared with ICH<sub>2</sub>SnBu<sub>3</sub> and ICH<sub>2</sub>SnMe<sub>3</sub>.<sup>12</sup> The cyclopropanation of norbornene (9-fold excess) by ICH<sub>2</sub>SnBu<sub>3</sub> catalyzed by Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub> (25 mol %) yielded **8** in 71% yield (based on 33% conversion after 15 days). In addition, C<sub>2</sub>H<sub>4</sub>, CH<sub>2</sub>O, MeSnBu<sub>3</sub> ( $\delta_H$  CH<sub>3</sub> = 0.11) (24%), and CH<sub>2</sub>(SnBu<sub>3</sub>)<sub>2</sub> ( $\delta_H$  CH<sub>2</sub> = -0.16) (5%) were formed.<sup>13</sup>

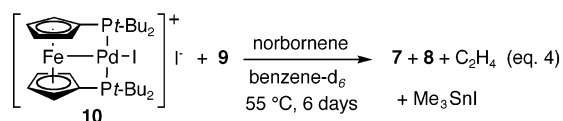


Further insights into the metal-carbenoid mechanism were gained from observations made with the deuterium-labeled *d*<sub>2</sub>-**6**. The *d*<sub>2</sub>-methylene singlet ( $\delta_D = 1.68$ ) of *d*<sub>2</sub>-**6** decreased while a set of signals appeared when treated with Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub> (25 mol %) and excess norbornene. <sup>2</sup>H NMR established the clean formation of tricyclo *d*<sub>2</sub>-**8**, CD<sub>2</sub>O, and C<sub>2</sub>D<sub>4</sub> (eq 3).<sup>14</sup>

The need for a Pd(0) catalyst in these reactions was confirmed by treating **6** with 50 to up to 200 mol % of P(*t*-Bu)<sub>3</sub> in the absence

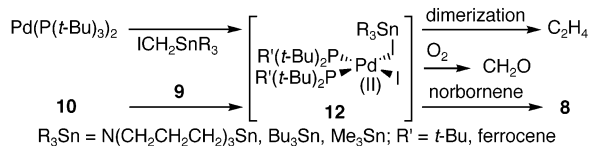
or presence of a 10-fold excess of norbornene. No decomposition of **6** or formation of cyclopropane **8**, ethylene, or formaldehyde was detected after several days at room temperature, ruling out phosphine-mediated decomposition mechanisms.

Envisioning that halopalladio-trialkylstannylalkane intermediates may be alternatively accessed under stoichiometric conditions via transmetalation from tin to Pd(II) led to the synthesis of  $\text{Me}_3\text{SnCH}_2\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2)_3\text{N}$  (**9**) ( $\delta_{\text{H}} \text{CH}_2 = -0.29$ ).<sup>15</sup> It was postulated that the stannatrane moiety of **9** would transmetalate preferentially with Pd(II)I<sub>2</sub> complexes, giving *cis*-Pd(II)I(CH<sub>2</sub>SnMe<sub>3</sub>) intermediates that would dimerize and cyclopropanate alkene.<sup>16</sup> Indeed, treatment of a benzene-*d*<sub>6</sub> solution of **9** and norbornene (9 equiv) with cationic [Pd(II)I]<sup>+</sup>I<sup>-</sup> complex **10** (1.05 equiv) at 55 °C for 6 days provided tricycle **8** in 36% yield, C<sub>2</sub>H<sub>4</sub> (not quantified), iodostannatrane (**7**), Me<sub>3</sub>SnI ( $\delta_{\text{H}} \text{CH}_3 = 0.11$ ) (59%), and Me<sub>4</sub>Sn ( $\delta_{\text{H}} \text{CH}_3 = 0.05$ ) (12%) (based on 80% conversion) (eq 4).<sup>17</sup>



As illustrated in Scheme 2, oxidative insertion of Pd(0) into the C–I bond<sup>18</sup> of **6**, ICH<sub>2</sub>SnBu<sub>3</sub>, or ICH<sub>2</sub>SnMe<sub>3</sub> and reaction of Pd(II) complex **10** with **9** converge to the key intermediate *cis*-iodo(methyltrialkylstannane)Pd(II) complexes **12**. These intermediates **12** rapidly react and are not detectable on the NMR time scale. Formation of ethylene occurs by dimerization of intermediate **12**.<sup>19</sup> The dimetallic **12** reacts with the residual O<sub>2</sub> present in solution to generate CH<sub>2</sub>O and with norbornene, providing tricycle **8**.<sup>20–22</sup>

#### Scheme 2



In conclusion, two complementary routes to sp<sup>3</sup>-*gem*-dimetallic iodopalladio(II)-trialkylstannylalkane complexes have been reported. These species exhibit carbenoid reactivity undergoing dimerization and alkene cyclopropanation, therefore validating the Busacca–Farina *cine*-substitution mechanism. Efforts to develop the synthetic potential of these species are now underway in our laboratories and will be reported in due course.

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**Supporting Information Available:** Procedures, <sup>1</sup>H, <sup>2</sup>H, and <sup>119</sup>Sn NMR spectra, and tables of crystallographic data for **10** (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (14) In some run, the dehalogenated byproduct, methylstannatrane, was detected.
- (15) Me<sub>3</sub>SnCH<sub>2</sub>Sn(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>N was selected for simplification of the <sup>1</sup>H NMR, and for its ease of synthesis and purification.
- (16) The transmetalation of alkylstannatrane with Pd(II) complexes was initially explored by treating (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub> with **6** to cleanly give (PPh<sub>3</sub>)<sub>2</sub>PdCl-(CH<sub>2</sub>) as observed by <sup>1</sup>H NMR. This Pd(II) complex decomposed over 5 days to C<sub>2</sub>H<sub>4</sub>, CH<sub>2</sub>O, and propene as reported by McCrindle, see ref 20.
- (17) The bidentate 1,1'-bis(di-*tert*-butylphosphino)ferrocene ligand (D-*t*-BPF) was rationally selected to lead to a *cis*-Pd(CH<sub>2</sub>SnMe<sub>3</sub>) complex following transmetalation, see: Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775–2789.
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- (19) No experimental data are available, suggesting the loss of halotrialkyltin prior to dimerization, cyclopropanation, or O<sub>2</sub> trapping.
- (20) Chloro(chloromethyl) Pd(II) complexes dimerize and undergo oxidation to CH<sub>2</sub>O under air, see: McCrindle, R.; Ferguson, G.; McAlees, A. J.; Arsenault, G. J.; Gupta, A.; Jennings, M. C. *Organometallics* **1995**, *14*, 2741–2748.
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- (22) When R<sub>3</sub>Sn is stannatrane (Scheme 2), **12** displays an enhanced carbenoid character in comparison to Bu<sub>3</sub>Sn and Me<sub>3</sub>Sn that is a direct reflection of its superior transmetalating ability; the carbene products were cleanly formed, and no or trace of dehalogenated byproduct was observed.

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