# Palladium(0) Catalyzed Coupling of trans-1,2-Bis(tri-n-butylstannyl)ethylene with Aromatic Halides: A Convenient Synthesis of Substituted trans- $\beta$ -Bromostyrenes.

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Summary: trans-\beta-Bromostyrenes have been conveniently prepared in moderate to high yield in a one-pot two-step sequence. trans-1,2-Bis(tri-n-butylstannyl)ethylene underwent a smooth palladium(0) catalyzed coupling reaction with 0.5 equivalents of aromatic bromide or iodide to furnish a *trans*- $\beta$ -stannylstyrene. This intermediate vinyl stannane, without isolation, was then converted to the substituted trans-bromostyrene on treatment with molecular bromine.

The benzylidene moiety, present in many natural products and other important compounds, is generally introduced via the Wittig reaction or one of its modifications.<sup>1</sup> In connection with an ongoing project in our laboratories, a scarcity of appropriately substituted aldehyde precursors and/or utilizable phosphoruscontaining reagents prompted us to investigate alternative methods for the introduction of this functionality in a stereodefined manner. In recent years several groups<sup>2</sup> have developed palladium mediated, regioselective carbon-carbon bond forming reactions which offer an improved procedure to introduce unsaturation.

Substituted  $\beta$ -stannyl and  $\beta$ -bromostyrenes are useful intermediates for the construction of benzylidene containing derivatives via palladium mediated processes. In particular, their value as substrates in various palladium(0) catalyzed coupling reactions for the production of numerous diene and eneyne systems has been well documented.<sup>2</sup> However, existing examples are limited to simple systems due to the lack of availability of substituted styryl substrates. Although various methods exist for their preparation, these often require preparation and purification of intermediate carbonyl containing or acetylenic compounds and isomeric mixtures are often encountered.<sup>3,4</sup> We wish to report here a mild one-pot synthesis of substituted trans- $\beta$ bromostyrenes from the corresponding aromatic bromides or iodides and readily prepared trans-1,2-bis(tri-nbutylstannyl)ethylene<sup>5</sup> (2) as outlined in Scheme I. Two distinct advantages our synthesis offers are: a) an abundance of commercially available substituted aromatic halides and b) functional group tolerance to the reaction conditions.

Recently Stille *et al.*<sup>6</sup> reported that any bromides and iodides reacted smoothly with tributylethenylstannane under palladium(0) catalysis to give  $\beta$ -unsubstituted styrenes. In an earlier report from the same laboratories<sup>7</sup>, and in a similar fashion, symmetrical stilbenes (5) were prepared by allowing 2 to react with two equivalents of an aromatic halide (1)(Scheme I-pathway c). We felt that if an excess of 2 was used in this reaction only one aromatic halide would couple thereby producing the monoarylvinyl stannane 3. The intermediate 3 could then be brominated<sup>4</sup> to produce the corresponding  $\beta$ -bromostyrene (4). Scheme I outlines our synthetic strategy.

Our initial experiments were encouraging. Using a six fold excess of  $2^5$  and allowing it to react with one equivalent p-bromoacetophenone in the presence of tetrakis(triphenylphosphine)palladium(0) in toluene at 100 °C followed by bromination at -20 °C produced the desired *trans-p*-acetyl-β-bromostyrene in 69% isolated yield. This experiment was repeated using 1.3 equivalents<sup>8</sup> of  $\underline{2}$  and the results were identical. Apparently, the second coupling reaction of the intermediate vinyl stannane ( $\underline{3}$ ) with unreacted aryl halide ( $\underline{1}$ ) is slower than the first coupling thus alleviating the need for excess  $\underline{2}$ .

This reaction was carried out in the presence of a number of functional groups, providing the  $\beta$ bromostyrene in yields ranging from 20% to 82% (Table I). In most cases minor amounts of stilbene byproduct 5 were isolated.

The intermediate vinylstannane  $\underline{3}$  could also be utilized<sup>9</sup> to produce a number of synthetically useful materials. A study of the *in situ* elaboration of these intermediates is currently underway.

### SCHEME I



X = Br or I

(a) 2 mole % Pd(PPh<sub>3</sub>)<sub>4</sub>, toluene, 100 °C; (b) Br<sub>2</sub>, CCl<sub>4</sub>, -20 °C; (c) Pd<sup>0</sup>, 2 equivalents of <u>1</u>.

#### **Experimental Procedure:**

A round bottom flask equipped with a magnetic stirrer was charged with the appropriate aromatic halide (1.6 mmol), trans-1,2-bis(tri-n-butylstannyl)ethylene<sup>5,8</sup> (1.26 g, 2.1 mmol), toluene (5.0 ml) and tetrakis(triphenylphosphine)palladium(0) (2 mole%; 0.037 g, 0.032 mmol) and the resulting solution (or slurry) was deoxygenated with a stream of argon. The reaction vessel was placed in an oil bath at 100-120 °C and stirred under argon at this temperature until TLC analysis indicated the starting halide was consumed (generally 0.25-1.0 hr). The intermediate vinyl stannanes produced generally possessed a higher  $R_f$  value than the starting halide. The reaction mixture (which generally turned to a dark brown or black slurry) was then cooled to -20 °C and treated dropwise with a 1 M solution of bromine in carbon tetrachloride.<sup>4</sup> This reaction was monitored closely by TLC analysis to ensure excess bromine did not react with the newly produced double bond.

Br R				
<u>4</u> Entry (4)	R≈	Workup Method	% Yield of $4^{11}$	<sup>1</sup> H NMR Vinyl Region (CDCl <sub>2</sub> : δ ppm)
a	o-Ac	Α	56	7.68 (d <sup>a</sup> , 14 Hz), 6.63 (d, 14 Hz)
b	<i>p</i> -Ac	Α	69	7.15 (d, 14 Hz), 6.94 (d, 14 Hz)
с	o-OMe	Α	33	7.32 (d, 14 Hz), 6.92 (d <sup>a</sup> , 14 Hz)
d	<i>m</i> -OMe	Α	29	7.07 (d, 14 Hz), 6.75 (d, 14 Hz)
e	<i>p-</i> OMe	Α	20	7.02 (d, 14 Hz), 6.59 (d, 14 Hz)
f	p-NO2	Α	82b	Br <sup>c</sup> : 7.69 (d <sup>a</sup> , 14 Hz), 7.58 (d, 14 Hz)
				I <sup>c</sup> : 7.49 (d, 14 Hz), 7.35 (d, 14 Hz)
g	p-CF3	В	58	7.10 (d, 14 Hz), 6.85 (d, 14 Hz)
h	p-CH <sub>2</sub> OH	В	65	7.09 (d, 14 Hz), 6.76 (d, 14 Hz)
i	p-CH <sub>2</sub> CN	В	68	7.07 (d, 14 Hz), 6.79 (d, 14 Hz)
j	p-CO <sub>2</sub> Et	В	66	7.15 (d, 14 Hz), 6.92 (d, 14 Hz)
k	o-Ph	В	62	7.05 (d, 14 Hz), 6.67 (d, 14 Hz)
	l			
1	p_0 0	В	47	7.11 (d, 14 Hz), 6.80 (d, 14 Hz)
	Ţ,			
m	P <sup>S</sup> ∕S	Α	69	7.07 (d, 14 Hz), 6.76 (d, 14 Hz)
n	~ 2-pyridyl	Δ	42	738 (d 14 Hz) 714 (d 14 Hz)
11	- z-pynayi	n	42	7.38 (u, 14 MZ), 7.14 (u, 14 MZ)

TABLE I. Synthesis of *trans*- $\beta$ -bromostyrenes (4).

a) Partly obscured by aromatic protons.

b) A 1:1 mixture of the iodide and bromide was obtained probably due to:  $Bu_3SnI + Br_2 \rightarrow Bu_3SnBr + IBr$ . The product ratio was determined by GCMS.

c) d<sup>6</sup>-acetone.

<u>Workup A</u>: The reaction mixture was warmed to room temperature and volatile components were removed at reduced pressure. The mixture was flash chromatographed on silica gel, eluting first with hexane to remove the tri-n-butyltin bromide by-product, then with an appropriate ether/hexane mixture. The product generally was of adequate purity for use in further reactions.

<u>Workup B</u>: The reaction mixture was warmed to room temperature and then diluted with ether. The residue was treated with 20% aqueous KF solution<sup>10</sup> (2.0 ml) and stirred vigorously for 30 minutes. The ether/toluene phase was decanted from the solid tin fluoride polymer/aqueous phase and the solvent was removed at reduced pressure on a rotary evaporator. The residue was purified by flash chromatography, recrystallization, or distillation.

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