## COMMUNICATION

## Ligand effects on the stereochemistry of Stille couplings, as manifested in reactions of Z-alkenyl halides<sup>†</sup>

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Unexpected losses in stereochemistry from Stille reactions involving Z-alkenyl halides have been shown to be ligand dependent. A new set of reaction conditions has been developed that, in most cases, leads to highly stereoselective crosscouplings under mild conditions, along with improved yields.

Stille couplings are among the most useful and powerful tools for the synthesis of complex molecules.<sup>1</sup> The attractiveness of organostananes likely derives from their high chemoselectivity and tolerance towards most functional groups.<sup>2</sup> There has been much effort over the last two decades towards optimization of reaction conditions, which has resulted in enhanced yields and broad substrate tolerance.<sup>3</sup> However, there are few investigations that focus on the stereochemistry of Stille couplings with alkenyl halides, in particular, Z-alkenyl halides. Thus, while the literature is rich with studies on the effects of external additives (*e.g.*, the copper effect<sup>4a</sup>), the prevailing assumption insofar as the mechanism is concerned remains that the overall sequence takes place with net double bond retention of substrate geometry and is independent of catalyst.<sup>4</sup>

Scattered reports have appeared over time, each noting that erosion of stereochemistry during a Stille coupling of a Z-alkenyl halide had occurred, albeit under varying conditions.<sup>5</sup> Thus, we set out to determine if the stereoselectivity of Stille couplings, as with Negishi<sup>6</sup> and Suzuki–Miyaura<sup>7</sup> reactions, is also ligand-dependent. If so, could a new set of conditions be found that would allow for the yield and extent of Z-stereoretention to be maximized (Scheme 1)? In this report we describe our findings on both fronts.

$$R \xrightarrow{} + Bu_3Sn-R' \xrightarrow{} DMF \text{ or THF} R' \xrightarrow{} R' + R \xrightarrow{} R'$$

Scheme 1 Stille couplings of Z-alkenyl halides.

An initial test reaction between mostly Z- $\beta$ -bromostyrene 1 (Z : E = 96 : 4) and vinyltributylstannane 2, catalyzed by Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, was carried out in THF at room temperature

**Table 1** Ligand effects on Stille couplings of Z- $\beta$ -bromostyrene<sup>*a,b*</sup> Ph + SnBu<sub>3</sub> catalyst Ph

	1 <sup>Br</sup> 2	24 h	3	
Entry	Catalyst	Conditions	Yield of $Z^{c}$ (%)	$Z/E^c$
1	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	А	45	86/14
2	Pd(PPh <sub>3</sub> ) <sub>4</sub>	А	19	36/64
3	$Pd(P(o-Tol)_3)_2$	А	2	4/96
4	$Pd(P(o-Tol)_3)_2$	А	$96(83)^{d,e}$	4/96
5	$Pd(P(t-Bu)_3)_2$	А	26	36/64
6	$Pd(dba)_2 + 2P(2-Furyl)_3$	А	22	57/43
7	Pd(dppf)Cl <sub>2</sub>	А	33	83/17
8	PEPPSI	А	38	93/7
9 <sup>f</sup>	PEPPSI	А	40	92/8
$10^g$	PEPPSI	А	54	92/8
$11^{g}$	PEPPSI	А	$92(77)^{d,h}$	92/8
12	$1/2Pd_2(dba)_3 + 2P(o-Tol)_3$	В	48	48/52
13	PdCl <sub>2</sub> (MeCN) <sub>2</sub>	В	6	70/30
	Ph + O 1 Br + 4 SnE	catalyst Bu <sub>3</sub> 24 h	→ Ph 5	
14	Pd(PPh <sub>2</sub> ) <sub>2</sub> Cl <sub>2</sub>	А	20	85/15
15 <sup>i</sup>	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	В	48	85/15
$16^g$	PEPPSI	А	9	90/10
$17^{i}$	$1/2Pd_{2}(dba)_{3} + 2P(o-Tol)_{3}$	В	86	96/4
18	$1/2Pd_2(dba)_3 + 2P(o-Tol)_3$	В	$96(87)^{h}$	96/4
19	$Pd(P(o-Tol)_3)_2$	В	$95(84)^{h}$	95/5
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<sup>*a*</sup> A: β-bromostyrene (0.250 mmol), organostannane (0.275 mmol), Pd catalyst (0.005 mmol; 2 mol % for entries 1–11, or 0.010 mmol, 4 mol %, for entries 14, 16), THF (1.0 mL), rt, 24 h. B: β-bromostyrene (0.250 mmol), organostannane (0.275 mmol), Pd catalyst (0.010 mmol), K<sub>2</sub>CO<sub>3</sub> (0.500 mmol), DMF (1.0 mL), rt. <sup>*b*</sup> The *Z/E* ratio of 1 is 96/4. <sup>*c*</sup> The yield of *Z*-product and *Z/E* ratio determined by GC/MS and <sup>1</sup>H NMR on crude products. <sup>*d*</sup> At 45 °C. <sup>*e*</sup> Isolated yield of *E*-product. <sup>*f*</sup> 2.0 equiv. of LiCl is used. <sup>*g*</sup> 2.0 of equiv. K<sub>2</sub>CO<sub>3</sub> is used. <sup>*h*</sup> Isolated yield of *Z*-product. <sup>*i*</sup> No K<sub>2</sub>CO<sub>3</sub>.

(Table 1, entry 1). While a modest yield (45%) was obtained, more interesting was the noticeable loss of >10% Z-olefin geometry. A series of commercially available ligands was subsequently screened to determine if this phenomenon is general, and to look for an alternative combination of catalyst and conditions that prevent such isomerization. Remarkably, almost complete inversion from Z- to E-diene **3** took place under the influence of Pd(P(o-Tol)<sub>3</sub>)<sub>2</sub><sup>8</sup> as catalyst, although mild heating to 45 °C was needed to achieve full conversion (entries 3, 4). Although both Pd(P(t-Bu)<sub>3</sub>)<sub>2</sub> and Pd<sub>2</sub>(dba)<sub>3</sub>/P(o-Tol)<sub>3</sub> also led to full consumption

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of bromide, poor yields of *Z*-**3** were obtained due to significant isomerization to *E*-**3** (entries 5, 12) and homecoupling (entry 5). PEPPSI<sup>9</sup> was an effective ligand for maintaining most of the initial *Z*-olefin geometry. The yield could be further improved by addition of  $K_2CO_3$ , along with gentle heating (entries 8–11).

In reactions of the corresponding 2-furylstannane **4**, changing the solvent from THF to DMF gave better results (entries 14, 15).<sup>5a,b</sup> Again,  $K_2CO_3$  (2 equiv.) appeared to enhance yields (compare entries 17 vs. 18), although its use with catalyst system  $Pd_2(dba)_3/P(o-Tol)_3^{10}$  led to better results than did PEPPSI using this stannane (compare entries 16 vs. 18).

Based on the results above, selected ligands on palladium were used as catalyst systems in a variety of Stille couplings (Table 2). These additional data are in line with those obtained in the model study (vide supra); i.e., that the level of erosion of stereochemical integrity in couplings of Z-alkenyl halides is dependent upon the ligand. In most cases, Pd<sub>2</sub>(dba)<sub>3</sub>/P(o-Tol)<sub>3</sub> (III) in DMF led to the desired products in high yields, with little-to-no isomerization being observed during these reactions; unexpectedly, however, the combination of  $\beta$ -bromostyrene and a vinylstannane did not follow this trend (see Table 1, entry 12). Using catalyst  $Pd(PPh_3)_2Cl_2$  (I), Z-olefin geometry can be compromised depending upon educt (entries 1, 9, 13, 16). Surprisingly, Z-1-iodooctene was converted almost entirely to E-6 in the presence of  $Pd(P(t-Bu)_3)_2$  (IV) (entry 6). Couplings under the influence of commonly used catalyst PdCl<sub>2</sub>(MeCN)<sub>2</sub> (II) displayed variable extents of both conversion, and maintenance of Z-stereochemistry. As examples, products 5 and 9 showed significant losses in Z-olefin geometry (entries 2, 17). Only in the case of entry 18 did Pd<sub>2</sub>(dba)<sub>3</sub>/P(o-Tol)<sub>3</sub> (III) fail to cleanly yield Z-9. Further optimization of reaction conditions by applying mild heat (45 °C) enhanced reaction rates such that complete conversion could be achieved in two hours in the presence of less catalyst (2 mol %), and without isomerization (entries 4, 12).

When cat.  $Pd_2(dba)_3/P(o-Tol)_3/K_2CO_3$  was applied to couplings of  $\beta$ -bromostyrene with both phenyltributyltin and tetrabutyltin in DMF at room temperature, only a trace of the desired product was formed in the latter case. Raising the temperature to 100 °C improved the yield (Table 2, entries 22–27, conditions D). The combination of  $Pd_2(dba)_3/P(o-Tol)_3$  (III) also proved to be the best choice for maintenance of Z-stereochemistry. However, although all  $\beta$ -bromostyrene was consumed, homocoupling was extensive in both cases, leading to modest yields of Z-11 and Z-12.

Reactions between Z-alkenyl halides and E-alkenylstannanes were also conducted using several common catalysts (entries 28–31). Remarkably, ligand effects with respect to stereochemistry were virtually nonexistent. Best results were obtained using Pd(MeCN)<sub>2</sub>Cl<sub>2</sub>/K<sub>2</sub>CO<sub>3</sub> at 45 °C to afford the desired product **13** (entry 30).<sup>11</sup> Cross-coupling of (Z)-((6iodohex-5-enyloxy)-methyl)benzene with (E)-3-(tributylstannyl)allyl acetate catalyzed by Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> led to a 24% loss of Z-stereochemistry (entry 32), while use of either Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> (**II**) or Pd<sub>2</sub>(dba)<sub>3</sub>/P(o-Tol)<sub>3</sub> (**III**), respectively, provided the stereoisomerically pure Z-product, Z-**14** (entries 33, 34).

As reported by Farina,<sup>12</sup> the reaction between Z-triflate **15** (G = OTf) and arylstannane **16** is a particularly challenging example, as this coupling led to almost complete isomerization to *E*-product **17** using Pd<sub>2</sub>(dba)<sub>3</sub>/AsPh<sub>3</sub> (Table 3, entry 1). By switching to Pd<sub>2</sub>(dba)<sub>3</sub>/P(o-Tol)<sub>3</sub>/K<sub>2</sub>CO<sub>3</sub> in DMF at 100 °C,

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**Table 2** Ligand effects on Stille couplings of various Z-alkenyl halides<sup>a</sup>

	R	∽x	+ R	l <sup>1</sup> −SnBu <sub>3</sub>	PdL <sub>n</sub>	->	R <sup>1</sup>	
Entry	Х	$PdL_n^b$	Conditions	Product		Yield o	of $Z^c$ (%)	$Z/E^c$
$1^d$	Br	I	А	•	^	29		30/70
$2^d$	Br	П	В		2	20		29/71
$3^d$	Br	Ш	В		5	$96(87)^{e}$		96/4
$4^d$	Br	Ш	С	5		96(85) <sup>e</sup>		96/4
5	Ι	I	А	_		97(89) <sup>e</sup>		98/2
6	Ι	IV	А	n-C <sub>e</sub> H <sub>12</sub>		$91(76)^{e}$	J	9/91
7	Ι	V	А		/ J	71		93/7
8	Ι	III	В	6	$\checkmark$	$99(92)^{e}$		99/1
$9^g$	Ι	Ι	А			42		86/14
$10^g$	Ι	Π	В		W O	95		95/5
$11^g$	Ι	III	В			96(86) <sup>e</sup>		96/4
$12^g$	Ι	Ш	С	EtO C		96(88) <sup>e</sup>		96/4
13	Ι	I	А			68		89/11
14	Ι	Π	В	/~/		95		95/5
15	Ι	Ш	В		OBn	99(95) <sup>e</sup>		99/1
				8				
$16^{h}$	Ι	I	А	_	_	36		48/52
$17^{h}$	Ι	II	В		-~~.	68		68/32
18 <sup>h</sup>	I	Ш	В	$\langle \rangle$	Ŵ	80(69) <sup>e</sup>		80/20
10				<u> </u>	Ph			00/1
19	I	I	A	.OBn		99		99/1
20	I	II	В		Ph	99		99/1
21	I	111	В			99(84) <sup>c</sup>		99/1
$22^d$	D.	т	$\mathbf{D}^{i}$		,	24		16/51
$2^{2}$	DI Dr	п	D	/~	Dh	24 52		<u>40/34</u> 91/10
23 $24^d$	DI Dr	II III	D		FII	52 64(55) <sup>e</sup>		06/4
24	DI	111	D	Ph 1	1	04(33)		90/4
25 <sup>a</sup>	Br	I	$\mathbf{D}^{\prime}$	1	$\sim$	2		41/59
$26^{d}$	Br	Π	D	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		68		89/11
27 <sup>d</sup>	Br	III	D	<sup></sup> h 12	2	44(39) <sup>e</sup>		95/5
28	Ι	I	А		~	42		99/1
29	Ι	П	В			82(73) <sup>e</sup>		99/1
30	Ι	Π	$\mathbf{C}^{j}$		~	93(84) <sup>e</sup>		99/1
31	I	ш	В	1	3	73		99/1
32	Ι	I	А		•	64		75/25
33	Ι	Π	В	/m/		99(93) <sup>e</sup>		99/1
34	Ι	III	В		OBn	99(90) <sup>e</sup>		99/1
				$\sim$		. /		

<sup>*a*</sup> A: alkenyl halide (0.250 mmol), organotin reagent (0.275 mmol), Pd catalyst (0.01 mmol), THF (1.0 mL), reflux, 24 h. B: alkenyl halide (0.250 mmol), organotin reagent (0.275 mmol), Pd catalyst (0.01 mmol), K<sub>2</sub>CO<sub>3</sub> (0.500 mmol), DMF (1.0 mL), rt, 24 h. C: alkenyl halide (0.250 mmol), organotin reagent (0.275 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.0025 mmol), P(*o*-Tol)<sub>3</sub> (0.01 mmol), K<sub>2</sub>CO<sub>3</sub> (0.500 mmol), DMF (1.0 mL), 45 °C, 2 h. D: β-bromostyrene (0.25 mmol), organostannane (0.30 mmol), Pd catalyst (0.010 mmol), DMF (1.0 mL), K<sub>2</sub>CO<sub>3</sub> (0.500 mmol), 100 °C, 24 h. <sup>*b*</sup> I: Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, II: Pd(MeCN)<sub>2</sub>Cl<sub>2</sub>, III: Pd<sub>2</sub>(dba)<sub>3</sub>/P(*o*-Tol)<sub>3</sub>, **IV**: Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub>, V: PEPPSI. <sup>*c*</sup> The yield of *Z*-product and *Z*/*E* ratio of β-bromostyrene is 96/4. <sup>*e*</sup> Isolated yield. <sup>*f*</sup> The *Z*/*E* ratio of 1-(2-iodovinyl)cyclohex-1-ene is 97/3. <sup>*i*</sup> No K<sub>2</sub>CO<sub>3</sub>. <sup>*i*</sup> The reaction time is 8 h.

the Z-olefinic product remained highly favored (89:11). Essentially complete retention of Z-geometry was observed when the iodo-analog **18** (G = I) was coupled with the same stannane, in this case at room temperature (entry 3).

 Table 3
 Ligand effects on the couplings of 15 and 18, with stannane 16<sup>a</sup>



 1 (15)  $Pd_2(dba)_3 + 8AsPh_3$ , NMP, overnight<sup>27</sup>
  $/2^c$  5/95 

 2 (15)  $Pd_2(dba)_3 + 4P(o-Tol)_3$ ,  $K_2CO_3$ , DMF, 8 h
  $76^{d,e}$  89/11 

 3 (18)  $Pd_2(dba)_3 + 4P(o-Tol)_3$ ,  $K_2CO_3$ , DMF, 16 h
  $86^{d,f}$  99/1 

<sup>*a*</sup> Catalyst (0.0025 mmol), **15** or **18** (0.25 mmol), **16** (0.30 mmol),  $K_2CO_3$  (0.50 mmol), solvent (1.0 mL), rt. <sup>*b*</sup> The ratio of *Z/E* determined by GC/MS and <sup>1</sup>H NMR on crude products. <sup>*c*</sup> Isolated yield of *E*-product. <sup>*d*</sup> Isolated yield of *Z*-product. <sup>*e*</sup> The reaction is performed at 100 °C. <sup>*f*</sup> (*Z*)-Ethyl 3-iodobut-2-enoate **18** is the substrate in place of **15**.



Scheme 2 Potential pathways for isomerisation in Stille couplings.

A plausible mechanism for ligand-related isomerization during Stille couplings of Z-alkenyl halides is illustrated in Scheme 2. The loss of Z-olefinic geometry may follow from a pathway involving either an anionic<sup>13</sup> or cationic<sup>14</sup> carbon as part of a zwitterionic-metal carbene (*e.g.* **20**) formed from an initial (likely stereospecific) oxidative addition to **19**. The Z/Eratio of products could also arise *via* prolonged reaction times in some cases, which may occur *via* reversible Pd–H elimination/re-addition.<sup>15</sup> Heating of reaction mixtures (compare Table 1, entry 14 with Table 2, entry 1) may contribute to both isomerization of intermediate **19** and/or formation of, and participation by, Pd–H, although Stille reactions in general oftentimes require some degree of heating.

In summary, the stereochemical outcome of Stille couplings involving Z-alkenyl halides and organostannanes has been shown to be highly variable, contrary to expectations, although fully consistent with related observations on Negishi<sup>6</sup> and Suzuki–Miyaura<sup>7</sup> couplings. In most cases, both Pd<sub>2</sub>(dba)<sub>3</sub>/P(o-Tol)<sub>3</sub> and Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> are the preferred catalysts for maintenance of Z-stereochemistry, as well as for their effectiveness in mediating highly efficient crosscouplings in DMF.

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PEPPSI (Pd-PEPPSI-IPr)

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