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Synthesis of (*Z*)-tributylstannyl enynes: systematic studies of Sonogashira cross-coupling reactions between (*E*)-1-iodovinyl-1-tributylstannanes and terminal acetylenes using amines or tetrabutylammonium hydroxide (TBAOH) as activator

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ABSTRACT

Sonogashira cross-coupling reactions involving (*E*)-iodo vinyl stannanes and terminal acetylenes were carried out in the presence of $Pd(PPh_3)_4$, CuI and several amines, affording (*Z*)-tributylstannyl enynes in moderate to good yields (62–91%). Utilizing the catalytic system containing $Pd(PPh_3)_4$ (5%), CuI (10%), and TBAOH (40% in aqueous media) as activator, better yields (72–91%) and lower reaction times were achieved.

Methods to prepare vinyl compounds containing two functional groups attached to the same C-sp^2, including 1,1-dibromoalkenes **7**,[1,2a] 1,1-diodoalkenes **8**,[2a,b] (*E*)-1,1-iodo vinyl stannanes **9**,[2a,c] (*Z*)-1,1-bromo vinyl stannanes **10**,[2a] and (*E*) or (*Z*)-1,1-organylchalcogen vinyl stannanes **3**–**4**[3] were extensively studied by our group and others (Scheme 1).[2a,3] In recent decades, these compounds emerged as powerful intermediates applied in the construction of di- and trisubstituted alkenes.[4–7]

The synthesis of conjugated enynes with defined stereochemistry is important, because these molecules have been found in natural products with interesting biological activity, such as calicheamycin (antitumor antibiotic),[8] terbinafine (antifungal agent),[9] alkaloid hachijodine G (cytotoxic toward P388 murine leukemia cells),[10] alkaloids 283A[11], and (−) -203A (inhibitors of nicotinic receptors).[12]

Among the methods applied to the formation of new carbon–carbon sp–sp^2 bond, the Stille, Sonogashira, Negishi, and Suzuki cross-coupling reactions, mediated by metal-catalysts, have proved efficient for the synthesis of enynes.[4]

Our research group has a strong interest in developing a novel and efficient method to synthesize compounds containing conjugated geminal enediyne systems[13–16] which can be used in the construction of molecules with electronic properties.[6]

We envisioned a synthetic route to obtain these compounds, involving a Sonogashira cross-coupling reaction to synthesize (*Z*)-tributylstannyl enynes type **14** from (*E*)-1,1-iodo vinyl stannanes **9**, followed by Corey-Stille cross-coupling reaction of **14** leading to geminal enediynes **16** (Scheme 2).

Although the Sonogashira reaction is effective to introduce an alkyne group into organic molecules, the major disadvantage of this coupling is the large amounts of amine used as solvent or co-solvent.[17] Furthermore, the nature of palladium catalysts is crucial to the success of the reaction.[18]

Myers and co-workers[19] reported the Sonogashira cross-coupling synthesis of (*Z*)-tributylstannyl enyne, from a (*E*)-1,1-iodo vinylstannane type **9**, as a precursor of the potent anticancer agent calicheamycin-enediyne N19999 A2. A catalytic system containing

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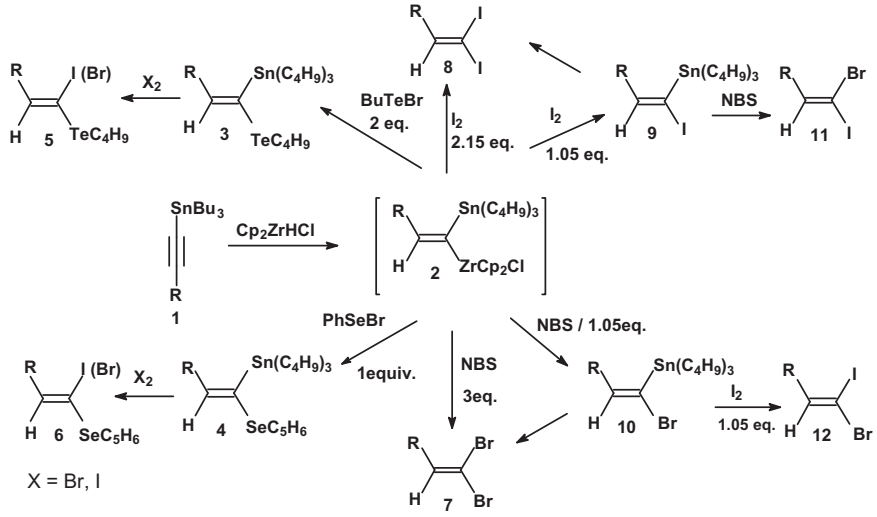
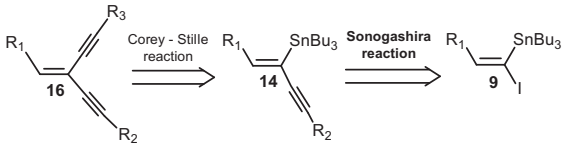
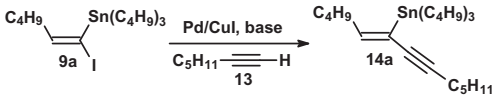


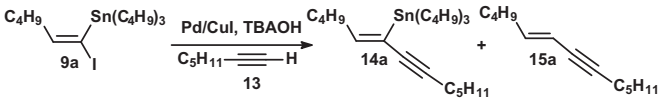
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

$Pd(PPh_3)_4$/CuI/Et_3N and a long reaction time (24 h) were necessary to complete the reaction. Moreover, the use of highly toxic and teratogenic benzene as solvent and the moderate yield achieved in the synthesis of the (*Z*)-enyne are strong disadvantages of the method.[19]

An alternate method to synthesize (*Z*)-tributylstannyl enynes was described by Cai et al.[20] In this case, it was necessary to use $Pd(PPh_3)_4$/CuI as a catalytic system, and pyrrolidine in large excess.

However, a systematic study using different palladium catalysts, activators, and other reaction conditions to reduce the reaction time and the amount of amine has not yet been described.[20]

Herein, we describe a systematic study aimed at the preparation of (*Z*)-tributylstannyl enynes via the Sonogashira cross-coupling reaction using (*E*)-1,1-iodo vinyl stannanes type **9** as the starting material, in a wide range of reaction conditions.

Initially, the cross-coupling of (*Z*)-1-iodo-1-tri(butyl)stannyl-1-hexene **9a** with 1-heptyne was examined, in order to determine suitable reaction conditions (Scheme 3; Table 1).

Table 1
Reaction conditions tested in the coupling of **9a** with 1-heptyne

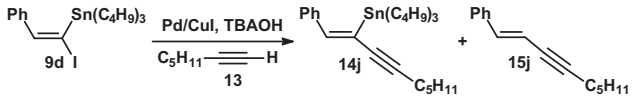
Entry	Catalytic system	Amine	Time (h)	% Yield[c]	
				9a	**14a**
1	A	Et_3N	3	0	3
2	A	Pyrrolidine	24	25	25
4	B	Pyrrolidine	7	40	5
5	C	Et_3N	11	30	11
6	C	Morpholine	30	30	4
7	C	Pyrrolidine	18	0	5
8	D	Et_3N	6	0	65
9	D	*n*-$BuNH_2$	22	0	3
10	D	DIPEA	17	0	8
11	D	Pyrrolidine	10	0	83
12	D	Piperidine	8	0	91
13	D	4-Methyl-piperidine	5	0	86
14	D	Morpholine	18	0	62
15	D	Pyrrolidine[b]	25	0	89
16	D	4-Methyl-piperidine [b]	1	—	—

[a] Reaction conditions: **9a** (1.0 mmol), **13** (2.0 mmol), amines (2.0 mmol) at room temperature, Catalytic System: A—$PdCl_2$ 10%/CuI 20%, B—$PdCl_2(MeCN)_2$ 5%/CuI 10%, C—$PdCl_2(PPh_3)_2$ 5%/CuI 10%, D—$Pd(PPh_3)_4$ 5%/CuI 10% and THF (3.0 ml) at room temperature.
[b] We used 1.0 mL of amines.
[c] Ratio detected by ^1H NMR (300 MHz) of the crude products.

Table 2
Reaction conditions tested in the coupling of **9a** with 1-heptyne

Entry	Solvent	Activator[b]	Time (h/min)	% Yield[d]	
				14a	**15a**
1	THF 4 mL	A	2 h	0	62
2	THF 4 mL	A	30 min	0	73
3	THF 4 mL/isopropanol 1 mL[c]	A	10 min	50	20
4	THF 4 mL	B	10 min	0	74
5	THF 4 mL/MeOH 3 mL[c]	A	10 min	89	0
6	THF 4 mL/EtOH 3 mL[c]	A	10 min	81	0
7	THF 4 mL/isopropanol 3 mL[c]	A	10 min	75	0
8	THF 4 mL/*t*-BuOH 3 mL[c]	A	10 min	65	10
9	DMF 4 mL	A	10 min	0	72

[a] Reaction conditions: **9a** (0.5 mmol), **13** (1.0 mmol), TBAOH (1.0 mmol) at room temperature, catalytic system used: $Pd(PPh_3)_4$ 5%/CuI 10%.
[b] Activator A: TBAOH in H_2O 40% (2.0 equiv); B: TBAOH in MeOH 25% (2.0 equiv).
[c] Alcohols were used to dilute the activator.
[d] Ratio detected by ^1H NMR (300 MHz) of the crude products.

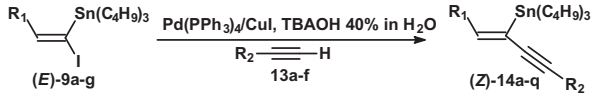


Scheme 5.

Table 3
Coupling reaction of 9d with 1-heptyne[a]

Entry	Solvent	Activator	Time (min)	% Yield [f]	
				14j	15j
1	THF 4 mL/MeOH 3 mL[b]	A[c]	10	64	16
2	THF 4 mL/$(CH_3)_2COH$ 3 mL[b]	A[c]	10	48	32
3	THF 4 mL/MeOH 4 mL[b]	A[c]	10	67	13
3	THF 4 mL/MeOH 3 mL[b]	A[d]	10	75	5
4	THF 4 mL/MeOH 3 mL[b]	A[e]	10	16	64
5	THF 3 mL/MeOH 3 mL[b]	A[d]	10	75	5
6	THF 2 mL/MeOH 3 mL[b]	A[d]	10	84	3

[a] Reaction conditions: **9a** (1.0 mmol), **13** (2.0 mmol), TBAOH in H_2O 40% (2.0 mmol) at room temperature; catalytic system used: $Pd(PPh_3)_4$ 5%/CuI 10%; activator A: TBAOH in H_2O 40%.
[b] 3.0 ml MeOH or isopropanol was used to dilute the TBAOH 40% in H_2O.
[c] Dropwise addition (30 s).
[d] Dropwise addition (5.0 min).
[e] Instantaneous addition.
[f] Ratio detected by ^1H NMR (300 MHz) of the crude products.



Scheme 6.

The catalyst system $Pd(PPh_3)_4$ 5 mol % and CuI 10 mol % showed the best results (Table 1, entries 8–15). The most suitable amines for the synthesis of (*Z*)-tributylstannyl enynes were piperidine (entry 12), pyrrolidine (entries 11 and 15), 4-methyl-piperidine (entry 13), triethylamine (entry 8), and morpholine (entry 14).

When pyrrolidine was used in excess, the reaction time decreased and the yield increased (entry 15). On the other hand, by using 4-methylpiperidine in excess, decomposition of the starting material was observed (entry 16).

Tetrabutylammonium hydroxide (TBAOH) was also tested as an activating agent in the synthesis of (*Z*)-tributylstannyl enyne **14**.[17,21,22]

We examined several reaction conditions, using the catalyst system: $PdCl_2(PPh_3)_2$, $PdCl_2(PhCN)_2$, $Pd(PPh_3)_4$, and CuI as co-catalysts in the presence of tetrabutylammonium hydroxide (TBAOH). The $Pd(PPh_3)_4$ and CuI as co-catalysts gave the best results for preparation of the (*Z*)-tributylstannyl enyne **14a** (Scheme 4, Table 2, entries 5–7).

In order to avoid the formation of vinyl compound **15a** as a byproduct, detected in various cases (e.g., Scheme 4, Table 2), we carefully studied the effect of several different solvents on the product distribution.

By using THF and DMF (Table 2, entries 1, 2, 4 and 9) as solvent, the (*E*)-1-organyl-1-buten-3-yne **15a** was obtained exclusively. By adding methanol or ethanol as co-solvent, the reactions were faster and afforded only the (*Z*)-tributylstannyl enyne **14a** (Table 2, entries 5 and 6). Isopropanol and *t*-butanol were also employed as co-solvents but the best yield was obtained using methanol (Table 2, entries 5–8).

However, when the reaction conditions used in entry 5 (Table 2) were applied to synthesize **14j**, only the vinyl compound **15j** was obtained (Scheme 5). This motivated us to find more efficient reaction conditions for the synthesis of (*Z*)-tributylstannyl enyne type **14** from (*E*)-1,1-iodo vinyl stannanes **9**.

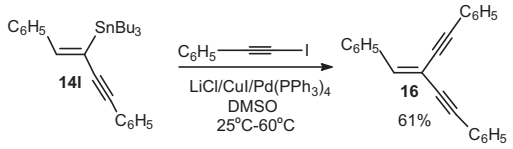
The rate of the solvent mixture THF/MeOH (2:3 v/v) (Table 3, entry 6) and dropwise addition (5 min) were crucial to decrease the formation of (*Z*)-vinyl compound **15j**. Therefore, we synthesized a wide range of (*Z*)-tributylstannyl enynes **14a–q** in order to explore the scope and limitations of this reaction (Scheme 6, Table 4).

Using the aromatic (*E*)-1,1-iodo vinyl stannanes **9d** as starting material (Table 4, entries 9–11), a small amount of vinyl compounds of type **15j** was detected. However, in all cases, the purification of the desired (*Z*)-tributylstannyl enynes **14j–l** was readily accomplished by flash chromatography.

Table 4
Synthesis of (*Z*)-tributylstannylenynes **14a–q**[33–37]

Entry	(*E*)-Iodo vinyl stannanes	R_1	R_2	Product[a]	% Yield
1	**9a**	n-C_4H_9	n-C_5H_{11}[b]	**14a**	89
2	**9a**	n-C_4H_9	$CHOH(CH_3)_2$[b]	**14b**	72
3	**9a**	n-C_4H_9	Ph[b]	**14c**	84
4	**9b**	n-C_6H_{13}	n-C_5H_{11}[b]	**14d**	91
5	**9b**	n-C_6H_{13}	$CHOH(CH_3)_2$[b]	**14e**	77
6	**9b**	n-C_6H_{13}	Ph[b]	**14f**	87
6	**9c**	$Cl(CH_2)_3$	n-C_5H_{11}[b]	**14g**	85
7	**9c**	$Cl(CH_2)_3$	$CHOH(CH_3)_2$[b]	**14h**	79
8	**9c**	$Cl(CH_2)_3$	C_4H_9[b]	**14i**	86
9	**9d**	Ph	n-C_5H_{11}[c]	**14j**	84
10	**9d**	Ph	$CHOH(CH_3)_2$[c]	**14k**	75
11	**9d**	Ph	Ph[c]	**14l**	82
12	**9e**		CH_2OCH_2Ph[b]	**14m**	72
13	**9e**		CH_2OH[b]	**14n**	76
14	**9f**	$PhCH_2OCH_2$	n-C_5H_{11}[b]	**14o**	85
15	**9f**	$PhCH_2OCH_2$	CH_2OH[b]	**14p**	79
16	**9g**	H	Ph[b]	**14q**	82

[a] Reaction conditions: **9a–f** (1.0 mmol), **13a–f** (2.0 mmol), THF (2.0 mL), TBAOH in H_2O 40% (2.0 mmol) at room temperature; catalytic system used: $Pd(PPh_3)_4$ 5%/CuI 10%, 3 mL MeOH was used to dilute the TBAOH 40% in H_2O.
[b] Dropwise addition of TBAOH (30 s).
[c] Dropwise addition of TBAOH (5.0 min).



Scheme 7.

The Sonogashira cross-coupling reaction using TBAOH as base occurred faster than with the other bases studied. Usually the reaction was completed within 10 min, as evaluated by thin-layer chromatography. A possible explanation is that TBAOH is a stronger base than the other amines used, and could also be acting as a phase transfer catalyst (PTC).[23–25]

With these results, we envision a possibility of applying (*Z*)-tributylstannyl enynes in the synthesis of enediynes. Conjugated enediyne systems, represented by 1,1-diethynylethenes (3-ethynyl-1-buten-3-ynes, *gem*-DEE)[16] type **16** (Scheme 7), emerged recently as a promising starting material for the synthesis of compounds with wide applications in non-linear optics (NLO),[26] macrocyclic ligands,[27] and polycyclic aromatic hydrocarbons (PAHs).[28] Few methods to prepare conjugated *gem*-enediynes have been reported, and most use Sonogashira metal palladium catalyzed cross-coupling reactions of 1,1-dibromo-1-alkenes with 1-alkynes.[6,29] Normally, in these processes bromoenynes are detected as byproducts and significant amounts of the starting material are recovered[29b,c] leading to low yield.[30] In contrast, the Sonogashira reactions of telluroketene acetals and 1-alkynes afforded the *gem*-enediynes in good yields.[13] However, vinyl organotelluride compounds have shown high toxicity and teratogenic effects.[31] Recently, Kabalka et al.[14] described an efficient method to synthesize conjugated *gem*-enediynes in high yield using palladium-catalyzed cross-coupling reactions of the readily accessible 1,1-dibromo-1-alkenes and stable potassium alkynyltrifluoroborates. However, these cross-coupling catalyzed metal reactions using 1,1-dibromo alkenes or telluroketene acetals as starting material are synthetically limited, always leading to the conjugated symmetrical *gem*-enediynes containing the same two alkynyl groups attached at the sp^2 carbon.[13,14]

We describe herein an application of the Corey-Stille cross-coupling reaction[32] for the synthesis of these compounds, represented by the conjugated *gem*-enediynes **16**.

We examined the reaction of (Z)-1,4-diphenyl-2-tributylstannyl-1-buten-3-yne **14l** (1.0 equiv) and 1-iodo-2-(phenyl) ethyne (1.5 equiv) in a homogeneous catalytic system containing CuCl (5.0 equiv), LiCl (6.0 equiv) in DMSO (8.0 mL) which furnished the conjugated *gem*-enediynes **16** in good yield (Scheme 7).[38,39]

In conclusion, Sonogashira cross-coupling reactions between (*E*)-1,1-iodo vinyl stannanes **9** and terminal acetylenes **13** using $Pd(PPh_3)_4$/CuI as catalytic system and aqueous TBAOH 40% as activator proved to be efficient in the preparation of (*Z*)-tributylstannyl enynes **14**. Conjugated *gem*-enediynes **16** were successfully synthesized using the Corey-Stille cross-coupling reaction of the (*Z*)-tributylstannyl enyne **14l** with 1-iodo-2-phenyl acetylene. A systematic study involving Corey-Stille cross-coupling of (*Z*)-tributylstannyl enynes with 1-iodo-2-organyl acetylenes to synthesize unsymmetrical *gem*-enediynes is in progress in our laboratory.

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33. *Typical procedure for the Sonogashira cross-coupling reaction with TBAOH*. To a solution of **9a** (0.467 g; 1.0 mmol), $Pd(PPh_3)_4$ (0.058 g; 0.05 mmol,), and CuI (0.019 g; 0.1 mmol), 1-alkyne **13** (0.192 g; 2.0 mmol), in THF (2.0 mL) at 25 °C, under a nitrogen atmosphere was added dropwise (according to Table 3), a solution of tetrabutylammonium hydroxide (TBAOH) (2.0 mmol, 40% aqueous solution) diluted with methanol (3.0 mL). The reaction was stirred at 25 °C for 10 min, extracted with ethyl acetate (3 × 15.0 mL), and washed with brine (4 × 10.0 mL). Next, the organic layer was dried over $MgSO_4$ and the solvent evaporated under vacuum. The crude product was purified by flash silica-gel chromatography using hexane as mobile phase to give pure **14a** as light yellow oil. Yield: 89%. IR (neat, cm^{-1}) 2959; 2856; 2233; 1564; 1463; ^1H NMR (300 MHz, δ in $CDCl_3$): 0.90 (t, 15H, *J* = 7.1 Hz); 1.00 (t, 6H, *J* = 8.1 Hz); 1.29–1.58 (m, 24H); 2.03 (q, 2H, *J* = 7.1 Hz); 2.32 (t, 2H, *J* = 6.9 Hz); 6.62 (t, 1H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, δ in $CDCl_3$): 10.86; 13.69; 13.99; 19.80; 22.31; 22.52; 27.38; 29.03; 29.07; 31.25; 31.90; 35.24; 84.51; 91.35; 124.01; 151.38.
34. *(Z)-1-Hexyl-2-tributylstannyl-4-phenyl-1-buten-3-yne* **14f** as light yellow oil. Yield: 86%. IR (neat, cm^{-1}): 2920, 2854, 2179, 1582, 1464; ^1H NMR (300 MHz, δ in $CDCl_3$): 0.90 (t, 12H, *J* = 6.8 Hz); 1.08 (t, 6H, *J* = 8 Hz); 1.39–1.56 (m, 20H); 2.12 (q, 2H, *J* = 7.1 Hz); 6.62 (t, 1H, *J* = 7.7 Hz); 7.23–7.26 (m, 2H); 7.28–7.40 ppm (m, 3H). ^{13}C NMR (75 MHz, δ in $CDCl_3$): 11.02; 13.69; 22.61; 27.37; 28.96; 29.63; 31.79; 35.87; 90.67; 93.89; 123.28; 124.68; 127.21; 128.15; 131.25; 153.27. HRMS 445.1926 $(M-C_4H_9)^+$; 445.1917 ($C_{24}H_{37}Sn$ 2 ppm).
35. *(5Z)-2-Methyl-6-phenyl-5-(tributylstannyl)hex-5-en-3-yn-2-ol* **14k** as light yellow oil. Yield: 75%. IR (neat, cm^{-1}): 3350, 2854, 2179, 1582, 1464; ^1H NMR (300 MHz, δ in $CDCl_3$): 0.84 (t, 9H, *J* = 6.5 Hz); 0.90 (t, 6H, *J* = 6.5 Hz); 1.24 (sex, 6H, *J* = 6.5 Hz); 1.4 (qui, 6H); 1.59 (s, 6H); 1.94 (s, 1H), 7.20–7.22 (m, 2H), 7.26–7.33 (m, 3H), 7.76 (s, 1H). ^{13}C NMR (75 MHz, δ in $CDCl_3$): 11.68; 13.64; 27.32; 28.84; 31.69; 65.87; 87.10; 98.28; 127.3; 127.4; 127.8; 128.2; 139.9; 150.8. HRMS: 419.1392 $(M-C_4H_9)^+$; 419.1396 ($C_{21}H_{31}OSn$ 1.1 ppm).
36. *(Z)-1-(3-Cloro-propyl)-4-butyl-2-tributylstannyl-1-buten-3-yne* **14i** as light yellow oil. Yield: 86%. IR (neat, cm^{-1}): 2929, 2194; 1587; 1463. ^1H NMR (300 MHz, δ in $CDCl_3$): 0.88–0.93 (m, 12H); 1.04 (t, 6H, *J* = 7.1 Hz); 1.34 (sex, 8H, *J* = 7.1 Hz); 1.52 (qui, 8H, *J* = 6.9 Hz); 1.86 (qui, 2H, *J* = 7.1 Hz); 2.20 (quart,

2H, J = 7.1 Hz); 2.34 (t, 2H, J = 7.1 Hz); 3.54 (t, 2H, J = 6.3 Hz); 6.58 (t, 1H, 7.3 Hz). ^{13}C NMR (75 MHz, δ in $CDCl_3$): 10.86; 13.69; 17.47; 22.06; 27.34; 29.03; 31.31; 32.48; 44.44; 84.19; 92.24; 126.21; 148.77. HRMS: 417.1368 $(M-C_4H_9)^+$; 417.1370 ($C_{19}H_{34}ClSn$ 0.7 ppm).

37. *Tributyl(1-methylene-3-phenylprop-2-yn-1-yl)stannane* **14q** as light yellow oil. Yield: 82%. IR (neat, cm^{-1}): 2928, 2853; 2172; 1597; 1464. ^{1}H NMR (300 MHz, δ in $CDCl_3$): 0.89 (t, 9H, J = 7.1 Hz); 1.05 (t, 6H, J = 7.1 Hz); 1.34 (sex, 6H, J = 7.1 Hz); 1.56 (qui, 6H, J = 6.9 Hz); 5.61 (d, 1H, J = 3.43 Hz); 6.31 (d, 1H, J = 3.43 Hz). ^{13}C NMR (75 MHz, δ in $CDCl_3$): 10.32; 13.70; 27.58; 28.87; 93.12; 94.49; 124.27; 127.62; 128.2; 131.32; 134.12; 135.23. HRMS 361.0971 $(M-C_4H_9)^+$; 361.0978 ($C_{18}H_{25}Sn$ 2 ppm).

38. *Typical procedure for synthesis of conjugated gem-enediynes*. To a suspension of **14l** (0.487 g; 1.0 mmol), CuCl (0.495 g, 5.0 mmol), LiCl (0.254 g, 6.0 mmol), and tetrakis (triphenylphophine) palladium (0) (2.888 g; 2.5 mmol) in DMSO (8.0 mL) under nitrogen atmosphere was added a solution of 1-iodo-2-phenyl ethyne (0.345 g; 1.5 mmol) in DMSO (2.0 mL) and the reaction was stirred at 25 °C for 30 min. Next, the reaction temperature was raised to 60 °C and stirred for 60 min when water (5.0 mL) was added slowly. The reaction was extracted with ethyl acetate (3×15.0 mL) and washed with brine (4×10.0 mL). The organic phase was dried over $MgSO_4$, the solvent evaporated under vacuum, and the crude product purified by flash chromatography using hexane as mobile phase to give pure colorless oil **16**.

39. *1,1′-[2-(Phenylethynyl)-1-buten-3-yne-1,4-diyl]bisbenzene* **16**. Yield 61%. The NMR data are similar as published by Kabalka et al.[14] ^{1}H NMR (400 MHz, δ in $CDCl_3$): 7.20 (s, 1H); 7.30–7.45 (m, 9H); 7.51–7.60 (m, 4H); 7.95–8.01 (m, 2H); ^{13}C NMR (100 MHz, δ in $CDCl_3$) 86.80; 88.30; 89.15; 94.58; 103.27; 122.84; 122.91; 128.33; 128.45; 128.76; 129.08; 129.20; 131.67; 131.70; 135.71; 143.14.