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Selective Green Coupling of Alkynyltins and Allylic Halides to Trienynes *via* a Tandem Double Stille Reaction

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Abstract: The palladium-catalyzed reaction of alkynyltin compounds with allylic chlorides leads to a 2:2 coupling to give trienynes by regio- and stereoselective formation of three new C–C bonds. The reaction can be applied to different alkynyl and allylic fragments, providing a wide range of trienynes with different substitution patterns in very good yields. They can be prepared in a green way using recyclable polymeric tin alkynyls.

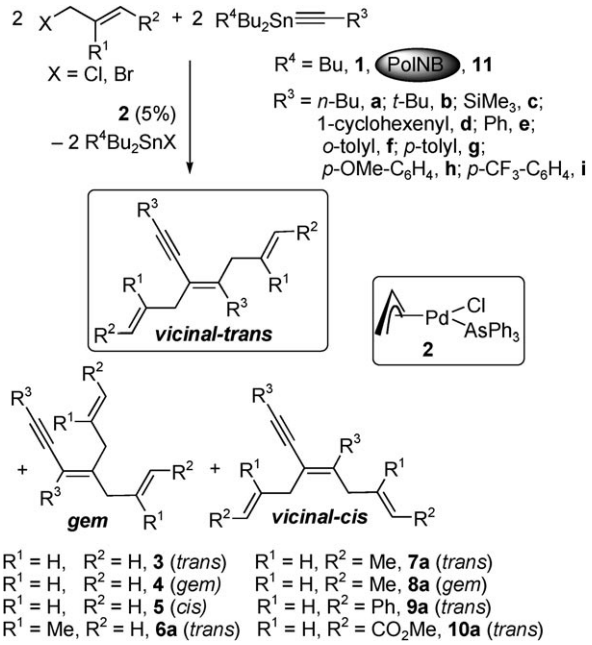
Keywords: C–C coupling; enynes; green chemistry; palladium; stannanes

The Stille reaction is one of the most powerful C–C building tools in organic synthesis.[1] It is still the reaction of choice for many transformations carried out in the presence of sensitive functional groups, since it is versatile and proceeds under mild conditions.[2] Its main drawback is the generation of toxic tin by-products, but there are some recent alternatives to overcome or alleviate this problem using polymeric recyclable tin reagents.[3,4] Although Stille couplings are well understood, certain combinations of reagents still give unexpected results. We report here the Pd-catalyzed reaction of alkynyltin compounds and allylic chlorides, a coupling that deviates from routine and results in the formation of trienynes, formally dimers of the expected 1:1 cross-coupling product.

There is increasing interest in the metal-catalyzed synthesis of enynes and oligoenynes, since highly unsaturated derivatives of this kind are useful building blocks for the synthesis of cyclic compounds, natural products, and materials.[5] The new reaction reported here provides a new and efficient tool for the synthesis of polyunsaturated molecules through C–C coupling, which complements the Sonogashira-type processes.[5,6]

The reactions of allylic halides with $Bu_3Sn(C{\equiv}CR^3)$ (**1a–i**) catalyzed by **2** (5% mol), lead to the formation of trienynes (Scheme 1). The *vicinal-trans* isomer (*trans* in Scheme and Table for short) is the only or the major reaction product. Two other isomers (*gem* and *vicinal-cis*) were also formed in several reactions (Scheme 1).

No 1,1-coupling product (allyl-alkynyl) was observed in any case. The reactions can be more conveniently carried out in a preparative scale using the polymeric tin reagents **11**. They were synthesized from copol-NB-NBSn(Bu)$_2$Cl, a vinylic polynorbornene functionalized with tin groups that we developed recently for its use in green Stille couplings.[3] This procedure allows the efficient purification of the reac-



Scheme 1. Synthesis of the trienynes and possible isomers.

Table 1. Reactions of $Bu_3SnC{\equiv}CR^3$ (**1**) and allylic halides catalyzed by **2** (entries n),[a] and preparative reactions of copol-NB-NBSn$(Bu)_2C{\equiv}CR^3$ (**11**) and allylic halides catalyzed by **2** (entries nPol).[b]

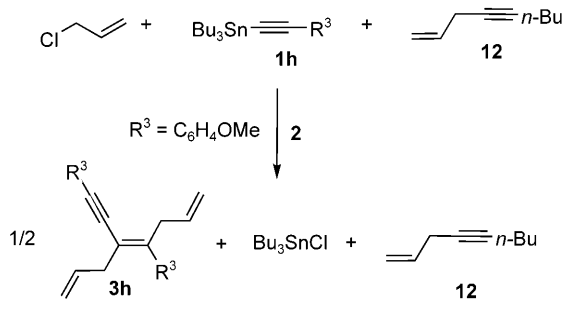
Entry	Tin reagent, R^3	R^1, R^2, X	**3**–**10**,% (25 °C, 8 h)[c]	Ratio *trans:gem:cis*	**3**–**10**,% (50 °C, h)[d]
1	**1a**, *n*-Bu	H, H, Cl	90	1:0:0	100 (8)
1Pol	**11a**, *n*-Bu	H, H, Cl		1:0:0	98 (24)
2	**1b**, *t*-Bu	H, H, Cl	34	18:1:0	58 (24)[e]
2Pol	**11b**, *t*-Bu	H, H, Cl		5.3:1:0	85 (24)
3	**1c**, Me_3Si	H, H, Cl	1	1:0:0	40 (96)
4	**1d**, 1-cyclohexenyl	H, H, Cl	39	2.2:1:0	63 (24)[e]
4Pol	**11d**, 1-cyclohexenyl	H, H, Cl		1:0:0	75 (24)
5	**1e**, Ph	H, H, Cl	73	5.3:1:0	92 (8)[e]
5Pol	**11e**, Ph	H, H, Cl		1:0:0	97 (24)
6	**1f**, *o*-tolyl	H, H, Cl	59	1:0:0	100 (8)
7	**1g**, *p*-tolyl	H, H, Cl	85	10:1:0	94 (8)[e]
8	**1h**, *p*-MeO-C_6H_4	H, H, Cl	100	1:0:0	100 (8)
8Pol	**11h**, *p*-MeO-C_6H_4	H, H, Cl		1:0:0	98 (24)
9	**1i**, *p*-CF_3-C_6H_4	H, H, Cl	37	3.6:1:1.7	100 (24)
9Pol	**11i**, *p*-CF_3-C_6H_4	H, H, Cl		6.8:1:0	98 (24)
10	**1a**, *n*-Bu	Me, H, Cl	55	1:0:0	100 (8)
10Pol	**11a**, *n*-Bu	Me, H, Cl		1:0:0	97 (24)
11	**1a**, *n*-Bu	H, Me, Cl	16	2.3:1:0	100 (24)
12	**1a**, *n*-Bu	H, Ph, Cl	45	1:0:0	100 (24)
12Pol	**11a**, *n*-Bu	H, Ph, Cl		1:0:0	70 (24)
13	**1a**, *n*-Bu	H, CO_2Me, Br	43	1:0:0	81 (24)[e]
13Pol	**11a**, *n*-Bu	H, CO_2Me, Br		1:0:0	98 (24)

[a] Reactions in $CDCl_3$. The conversion to **3**–**10** (%) was determined by ^1H NMR relative integration of the allyl protons in the allylic halide and in the products.
[b] Reactions in THF. Isolated yields.
[c] Molar ratio Sn:allyl halide = 1:1.
[d] Molar ratio Sn:allyl halide = 1.5:1.
[e] Total conversion was observed to give **3**–**10** in the% given, plus a monoallyl by-product (16% for entry 2, 8% for entry 5, 6% for entry 7 and 19% for entry 13), 23% of $R^3C{\equiv}C(allyl)C{=}C(R^3)C{\equiv}CR^3$ for entry 4 and allyltributylstannane (26% for entry 2 and 14% for entry 4).

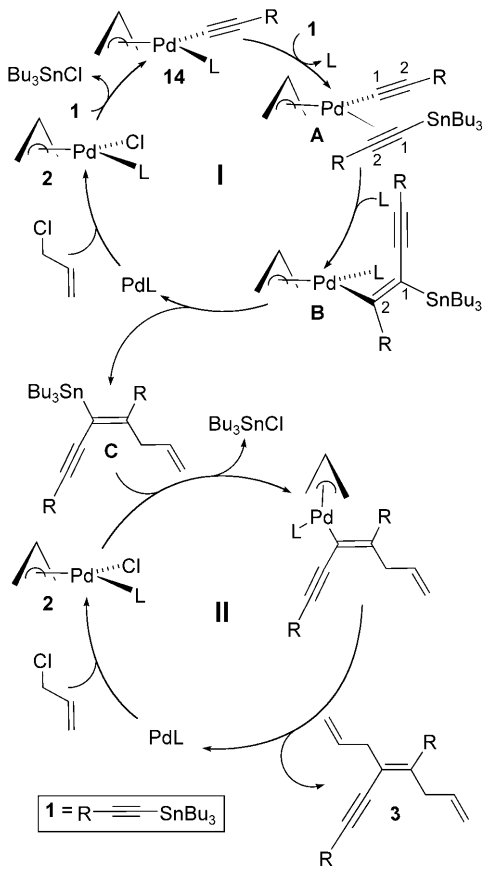
tion products, and the polymeric by-product can be recycled following the protocol reported before.[3]

Table 1 collects the conversions and isomeric ratio of the products for the reactions of several monomeric alkynyltins and allylic halides (entries n), as observed by NMR, at 25 °C (molar ratio **1**:allyl halide = 1:1), and under more stringent conditions (50 °C and **1**:allyl halide = 1.5:1). Benzoquinone was added as coupling promoter.[7,8] The reactions at 25 °C are fairly slow, which allows us to compare the reactivity of different substrates. An increase in the size of R^3 leads to lower rates (*cf.* entries 1 *vs.* 2, and 6 *vs.* 7). For R = aryl (entries 5–9), electron-donating substituents in the ring accelerate the reaction, while electron-withdrawing groups slow the reaction down. The reactions with polymers **11** give very good isolated yields (entries nPol) and in most cases (entries 4, 5, 9) the selectivity is even improved in comparison with the reactions of **1**.

The reaction is favored by the use of a labile ligand such as $AsPh_3$. Thus, complex $[Pd(\eta^3\text{-}C_3H_5)Cl(PPh_3)]$ is less active than **2**, and the reaction of entry 1 (Table 1) takes 2 days to reach 90% conversion (*cf.* 8 h when **2** is used). The 1,1-coupling product is not an intermediate in the reaction: When $CH_2{=}CH{-}CH_2{-}C{\equiv}C{-}Bu\text{-}n$ (**12**) was introduced as reactant in a coupling under conditions of entry 8, Table 1, the allyl chloride and **1h** were converted to **3h**, while **12** remained unaltered and no mixed-R (n-Bu/C_6H_4OMe) trienyne was formed (Scheme 2). The reaction does not occur *via* previous homocoupling of two alkynyl fragments. Thus the dialkyne n-Bu−C≡C−C≡C−Bu-n



Scheme 2. Coupling experiments in the presence of the 1:1 coupling product **12**.



Scheme 3. Proposed catalytic cycle for the synthesis of **3**. A monomeric alkynyltin and allyl chloride are depicted for simplicity. L is $AsPh_3$ or other ligand present (e.g., allyl chloride, benzoquinone, solvent, etc.) and can be different in each step.

(**13**) does not react with allyl chloride in the presence of **2**.

A plausible pathway for the formation of **3** is shown in the tandem process in Scheme 3. This proposal assumes that allyl-alkynyl couplings are slow,[8a,9] compared to allyl-vinyl couplings,[10] which is well known in the literature. The first step of the reaction could be confirmed by monitoring the reactions of **2** and five equivalents of **1a**, **d** by ^{1}H NMR at 243 K. Complete transformation of **2** into [Pd(η^3-C_3H_5)(C≡CR)($AsPh_3$)] (R = *n*-Bu, 1-cyclohexenyl **14a**, **d**) was immediately observed. Complex **14a** was also detected by ^{1}H NMR when the catalytic reaction of Table 1, entry 1 was monitored, showing that it is an intermediate preceding the rate-determining step.

Since the evolution of the reaction from **A** should be independent of L, the differences in rate of reaction observed will be due to the different displacement of the equilibrium **14**⇄**A**, and it is expected to be slower for stronger L donors (as observed in PPh_3 *vs.* $AsPh_3$). For the same L, the reaction rate should increase with the coordinating ability of the triple

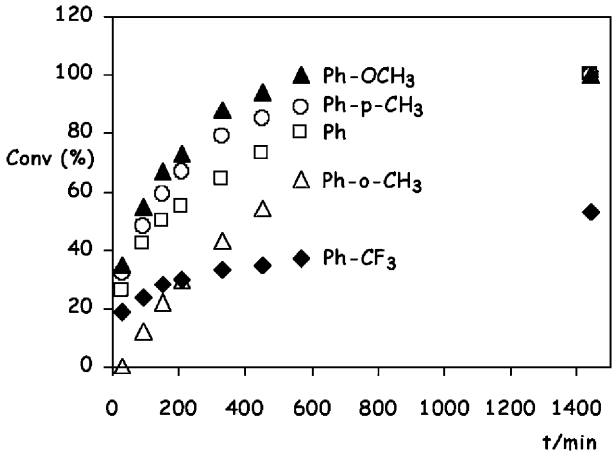
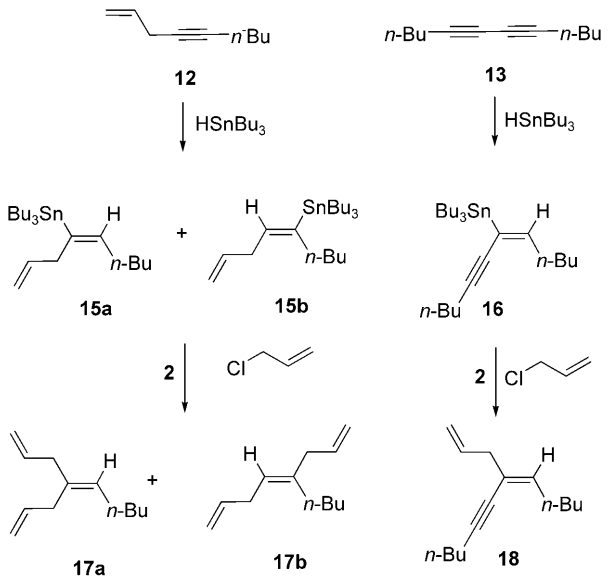


Figure 1. Plots of conversion (%) *vs.* time in the formation of **3** for alkynyltin derivatives **1e–i** (25 °C; molar ratio **1**:allyl halide = 1:1).

bond of the alkynylstannane. In this respect, the rate of formation of **3** was monitored for different aryl-substituted alkynyltins and the results confirm that electron-donating substituents accelerate the reaction (*p*-OMe > *p*-Me > H ≫ CF_3), whereas, for electronically equivalent substituents, an increase of the steric hindrance slows the reaction down (*p*-Me > *o*-Me) (Figure 1). The loss of selectivity with formation of **4** or **5** in some of the reactions can be explained at this point, by 1,2 insertion (see Scheme 3 for C labels) of the alkynyltin (giving **4**) or *trans*-2,1 insertion (giving **5**). Both types of regio- and sterochemistry have been observed in the insertion reactions of alkynes into M–C bonds.[11] The inclusion of the alkynyltin in a polymeric framework (Table 1, entries Pol) improves the selectivity to the *cis*-2,1 insertion, affording **3**; this is probably due to steric constraints in the π-coordination of the alkynyl stannane in **A**.

The last steps in the proposed pathway of Scheme 3 were checked by carrying out the Stille coupling of allyl chloride with two types of vinyltin derivatives with substitution patterns close to those of intermediate **C** (Scheme 3). These were synthesized by hydrostannation of **12**, which leads to a mixture of two isomeric compounds (**15a** and **15b**), or by hydrostannation of the dialkyne **13**, which affords **16** (Scheme 4). In the presence of an excess allyl chloride, benzoquinone, and **2** they give the coupling products in a fast reaction, confirming the feasibility of cycle **II**.

It is interesting to note that less selective results are obtained using other sources of alkynyl. When a mixture of 1-hexyne and a base such as potassium phosphate was used instead of the alkynyltin **1a**, only mixtures of **3a** and the 1:1 coupling product were obtained in low conversions (16% after 12 h at 50 °C). When the copper acetylide was used instead of **1a** the reaction also led to low conversions (24% after two days at 50 °C) and formation of equimolar mixtures of



Scheme 4. Stille coupling of vinyltin derivatives modelling the proposed intermediate **C**.

3a and the 1:1 coupling product.[12] This result can be fit in the frame of Scheme 3, considering that for alkynyls with slower coordination-insertion rates than alkynylstannanes, or with low solubility (such as the sparingly soluble copper alkynyls that makes them unlikely species as ligands) the 1:1 allyl-alkynyl coupling can become competitive with the process reported here.

In summary, a selective synthesis of trienynes, by the regio- and stereoselective coupling of alkynylstannanes and allyl halides, has been found. The reaction can be carried out in an environmentally clean way, using recyclable polymeric tin alkynyls. The trienyne products correspond to a 2:2 cross-coupling of the reagents, which occurs *via* a double Stille tandem reaction. The mechanistic study shows that the selectivity is due to the slowness of the allyl-alkynyl reductive elimination, compared to the fast rates of insertion of coordinated alkynylstannanes, and reductive elimination of allyl-vinyl fragments.

Experimental Section

General Considerations

^{1}H, $^{13}C\{^{1}H\}$, ^{19}F and ^{119}Sn NMR spectra were recorded on Bruker AC-300, ARX-300 and AV-400 spectrometers. Chemical shifts (in δ units, ppm) were referenced to Me_4Si (^{1}H and ^{13}C), $CFCl_3$ (^{19}F), H_3PO_4 (85%, ^{31}P) and $SnMe_4$ (^{119}Sn). The spectral data were recorded at 293 K unless otherwise noted. Mass spectra of the products were recorded on Agilent Tech. 5973 MS system. All the manipulations were carried out under an atmosphere of nitrogen using standard Schlenk techniques. Solvents were dried over and distilled from appropriate drying agents under nitrogen, prior to use. The reactants Bu_3SnCl, Bu_3SnH, phenylethynyltributyltin, dodeca-5,7-diyne, the organic halides and the terminal alkynes were obtained from commercial suppliers and used without further purification. The compounds Copol-NB-NB-Sn(Bu)$_2$Cl,[3] cuprous butylacetylide,[13] $[PdCl_2(PPh_3)_2]$,[14] $[\{Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)\}_2]$,[15] $[Pd(\eta^3\text{-}C_3H_5)Cl(AsPh_3)]$,[16] and $[Pd(\eta^3\text{-}C_3H_5)Cl(PPh_3)]$[16] were prepared according to literature methods.

2:2 Coupling Reactions using Copol-NB-NB-Sn(Bu)$_2$R: Preparation of 1,4-Dibutyl-3-propenylhept-6-en-1-yne (3a)

To a suspension of Copol-NB-NB-Sn(Bu)$_2$(C≡C−Bu-*n*) (2.400 g, 4.786 mmol), benzoquinone (0.0172 g, 0.160 mmol) and $[Pd(\eta^3\text{-}C_3H_5)Cl(AsPh_3)]$ (**2**, 0.0780 g, 0.160 mmol) in THF (75 mL), under N_2 was added the allyl chloride (0.2240 g, 3.191 mmol). The reaction mixture was heated at 50 °C for 18 h giving a dark solution. It was evaporated to dryness at room temperature, and the residue was washed with a mixture of *n*-hexane and MeOH and stirred for 30 min. The copolymer copol-NB-NBSn(Bu)$_2$Cl recovered was filtered, washed with MeOH, and air-dried; yield: 1.9839 g (83%). The filtrate was concentrated to 5 mL and filtered through activated carbon and silica gel. After distillation to remove the solvents, **3a** was obtained as a dark liquid; yield: 0.382 g (98%).The other 2:2 coupling products were obtained in a similar way starting from the corresponding copolymer and organic halide as collected in Table 1.

2:2 Coupling Reactions using Bu$_3$Sn(C≡C−R): Preparation of 3a

To a solution of Bu$_3$Sn(C≡C−Bu-*n*) (0.1362 g, 0.3674 mmol), benzoquinone (0.0020 g, 0.018 mmol) and the complex $[Pd(\eta^3\text{-}C_3H_5)Cl(AsPh_3)]$ (**2**, 0.0090 g, 0.0184 mmol) in $CHCl_3$ (6 mL), under N_2 was added the allyl chloride (0.0281 g, 0.3674 mmol). The reaction mixture was heated at 50 °C for 15 h giving a black solution. It was filtered thought activated carbon and Celite and evaporated to dryness at room temperature. The product was separated by column chromatography with silica gel using hexane as solvent. Treatment of the product with a saturated KF aqueous solution was necessary to separate Bu$_3$SnCl byproduct. After vigorous stirring for 30 min S*n*Bu$_3$F precipitated. The organic phase was extracted, dried with anhydrous $MgSO_4$, filtered through Celite and evaporated to dryness to afford a yellowish liquid (**3a**); yield: 0.0213 g (43%).

Supporting Information

Experimental details for the preparation of the tin derivatives **1**, copolymers **11** and compounds **15**–**18**, detection and characterization of complexes **14**, and characterization data of all compounds and selected NMR spectra are given in the Supporting Information.

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