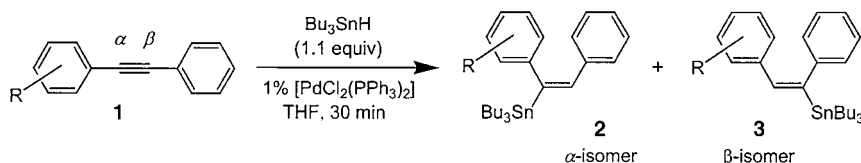# Ortho Substituents Direct Regioselective Addition of Tributyltin Hydride to Unsymmetrical Diaryl (or Heteroaryl) Alkynes: An Efficient Route to Stannylated Stilbene Derivatives**

Mouâd Alami,* Fréderic Liron, Marina Gervais, Jean-François Peyrat, and Jean-Daniel Brion

Table 1. Palladium-catalyzed hydrostannylation of unsymmetrical diaryl alkynes **1**.

Entry	R	Isolated yield [%]	
		2	**3**
1	**a**: p-NO$_2$	75	—[a]
2	**b**: p-CHO		98[b]
3	**c**: p-CO$_2$Et		81[b]
4	**d**: p-CH$_2$OH		86[b]
5	**e**: o-CHO	95	—[a]
6	**f**: o-CO$_2$Et	81	—[a]
7	**g**: o-CH$_2$OH	95	—[a]

[a] Stereoisomers **3** were not detected by ^{1}H NMR spectra in the crude reaction mixture. [b] Isolated yields of inseparable mixture of regioisomers. The ratios **2b**:**3b** 85:15, **2c**:**3c** 75:25 and **2d**:**3d** 50:50 were determined by ^{1}H NMR spectra in the crude reaction mixture.
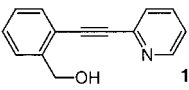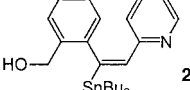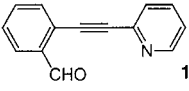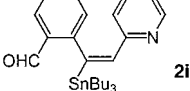
It is well known that the palladium-catalyzed hydrostannylation of internal alkynes proceeds in a stereoselective manner (cis addition) to yield vinyl stannanes.[1] Regiochemical control of this reaction, nevertheless, remains a challenge, especially in the case of unsymmetrical disubstituted alkynes. In this respect, to our knowledge, hydrostannylation of alkynes with two different aromatic (or heteroaromatic) rings is not known.[2] Herein, we describe the first highly regioselective Pd-catalyzed addition of tributyltin hydride to alkynes **1**, which is controlled by the ortho substituent at the aromatic ring, regardless of the electronic nature of this substituent. This reaction readily allows an efficient synthesis of stannylated, unsymmetrical 1,2-diaryl olefins **2**, which can be further transformed to variously substituted stilbenoid olefins. The latter are an interesting class of compounds, not only because of their occurrence as natural and biologically active substances,[3] but also for their interesting physical properties.[4]

Recently, we reported the effect of ortho substituents on the regioselectivity in the hydrostannylation of aryl-substituted alkynes.[5] It then occurred to us that this unprecedented ortho-directing effect (ODE) could be extended to control the regiochemistry of the reaction of unsymmetrical diaryl (or heteroaryl) alkynes **1**. Initially, we examined the hydrostannylation of diaryl alkynes bearing a para π-electron-withdrawing group, which induces strong polarization of the carbon–carbon triple bond. Thus, reaction of **1a** with Bu$_3$SnH in the presence of 1% [PdCl$_2$(PPh$_3$)$_2$] in THF gave **2a** in 75% yield as a single isomer, through an exclusive syn addition (entry 1, Table 1). This regioselectivity is expected as the palladium-catalyzed hydrostannylation of electron-deficient alkynes formally proceeds by conjugate addition of the hydride.[1c] In contrast to **1a**, hydrostannylation of diaryl alkyne derivatives **1b** and **1c**, which have a formyl or an

ethoxycarbonyl group (less powerful π-electron-withdrawing groups than the NO$_2$ moiety) in the para-position of the phenyl group, was less regioselective and gave a regioisomeric mixture with a preference for **2b–c** over **3b–c** (entries 2 and 3). In the case of alkyne **1d**, which contains a para σ-electron-donating group (R = p-CH$_2$OH, entry 4), the tributyltin hydride does not discriminate in its addition between the two carbon atoms of the triple bond, because the electronic effects of substituent groups through the aromatic ring appear to be minimal, and the reaction provided an inseparable 1:1 mixture of vinyl stannanes **2d** and **3d**. However, when the reaction was carried out with alkynes **1e–g**[6] with an ortho substituent, regardless of the electronic nature of the substituent (π-electron-withdrawing group: entries 5 and 6, or σ-electron-donating group: entry 7) a total selectivity was obtained in favor of the α isomers **2e–g** (Bu$_3$Sn group being α relative to the ortho-substituted aryl moiety, selectivity α:β = 100:0, entries 5, 6, and 7). Stereoisomers **3e–g** were not detected by ^{1}H NMR analysis in the crude reaction mixture. From alkynes **1e** and **1f**, a reasonable explanation of the remarkable level of regioselectivity lies in the electronic effects of ortho π-electron-withdrawing groups together with a possible intramolecular chela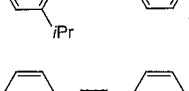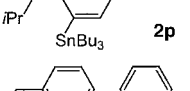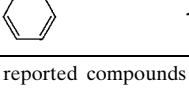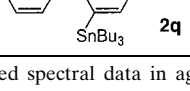tion between the palladium center and the heteroatom. However, the result obtained from alkyne **1g** with an ortho σ-electron-donating group strongly indicates that this α selectivity could not be controlled by the electronic effects of substituents.

Hydrostannylation of various unsymmetrical ortho-substituted diaryl alkynes, as well as of alkynes bearing a pyridyl moiety, was examined (Table 2). Total regioselectivity toward the formation of the α isomers **2** was obtained from diaryl (or heteroaryl) alkynes **1h–l** (entries 1 to 5, Table 2) bearing an ortho benzylic substituent with a heteroatom or an ortho halide substituent, except in the case of **1m** where small amounts of β isomer **3m** were formed (R = o-OMe, α:β 90:10, entry 6).[10] It is worth noting that the presence of an ortho benzylic substituent with a heteroatom or an ortho halide substituent on the aryl ring is not crucial to obtain regioselective addition of Bu$_3$SnH. Thus, hydrostannylation of **1o**, which bears an ortho methyl substituent, resulted mainly in

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Table 2. Synthesis of various stannylated stilbene derivatives and related compounds.[a]

Entry	Diaryl alkyne[b] 1	Vinyl stannane[c] 2	Yield[d] [%]
1	1h	2h	81
2	1i	2i	90
3	1j	2j	91
4	1k	2k	60
5	1l	2l	85
6	1m	2m	94[e]
7	1n	2n	81
8	1o	2o	91[e]
9	1p	2p	76
10	1q	2q	67

[a] All the reported compounds exhibited spectral data in agreement with assigned structures. The regiochemistry of entries 4 and 8 was established by comparison of compounds 2k and 2o with samples obtained by the following sequence: 1) reaction of 2g with CBr$_4$, PPh$_3$ in CH$_2$Cl$_2$ followed by amination[7] (Et$_2$NH, K$_2$CO$_3$, KI, MeCN) of the corresponding bromide afforded 2k. 2) Reduction of this bromide with NaBH$_4$ in DMSO[8] led to 2o. Regiochemical assignment of entry 3 was made as follows: 2j showed the same ^{1}H NMR spectra with sample obtained by condensation of 2e with EtMgBr. On the basis of these results, the regiochemistry shown was assumed for the products of entries 5–7, 9, and 10. [b] Diarylalkynes 1 were prepared according to ref. [9]. [c] All the compounds reported herein exhibited J values for the Sn–H coupling ranging from 60–70 Hz which are typical for cis configurations. [d] Yields are given for pure isolated products. [e] Isolated yields of inseparable mixture of regioisomers. Regioselectivity: 2m:3m 90:10, 2o:3o 93:7, as determined by ^{1}H NMR spectra of the crude reaction mixture.

the formation of the α adduct 2o (α:β 93:7, entry 8), although no stabilizing effect can occur between the Pd atom and the methyl substituent. On the other hand, the reaction with the corresponding alkyne with a methyl group in the para position gives almost a 1:1 mixture of the two regioisomeric adducts. More interestingly, the presence of bulky substituents in the diaryl alkyne derivatives (1n: R = OBn, entry 7 or 1p: R = iPr, entry 9) does not affect the hydrostannylation reaction and gives α adducts 2n and 2p selectively, in good yields (76–81 %), without any β adduct. Finally, the addition of Bu$_3$SnH also proved to be regioselective with alkyne 1q, in which the aromatic substituent on the triple bond is a 1-naphthyl group (entry 10).
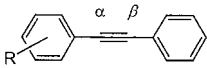
The regiochemical outcome for the selective formation of α adducts was established as follows. First, we showed that both sequences hydrostannylation–reduction (Path AB, Scheme 1) and reduction–hydrostannylation (Path BA, Scheme 1) of 1e and 1i, which have an ortho electron-withdrawing group, afforded the same α regioisomer 2g and 2h, respectively. Further evidence for the regioselectivity of compound 2g was obtained by its conversion into 4-benzylidene-2-benzopyran-3-one 5 by an intramolecular lactonization of the ester 4, which was readily obtained from 2g, according to Scheme 1.

The results obtained in the case of ortho-substituted diaryl alkynes 1 show that the preferential attack of the tin atom occurs mainly and sometimes exclusively at the C$_\alpha$ atom, regardless of the electronic nature of the ortho substituent (compare hydrostannylation of 1e and f with 1g; Table 1 and 1h with 1i; Table 2). This ODE can not be explained by only chelation between the palladium atom and the group containing the heteroatom, because ortho alkyl derivatives exhibit very high selectivity (entries 8 and 9, Table 2). Moreover, our results also suggest that the reaction is not governed by steric effects, as an increase in the size of the ortho substituent resulted in an exclusive α selectivity (compare hydrostannylation of 1m with 1n entries 6 and 7, Table 2, and 1o with 1p entries 8 and 9, Table 2). There may be others factors in the reaction which account for the observed regiochemistry. We found that ortho substituents induced dramatic variations in the ^{13}C NMR chemical shifts of the triple bond.[11] Table 3 summarizes the difference ($\Delta\delta_{C\beta\text{-}C\alpha}$) values found for the considered ortho- and para-substituted diaryl alkynes 1. Thus, ortho-substituted alkynes

Path A : hydrostannylation step
Path B : reduction step
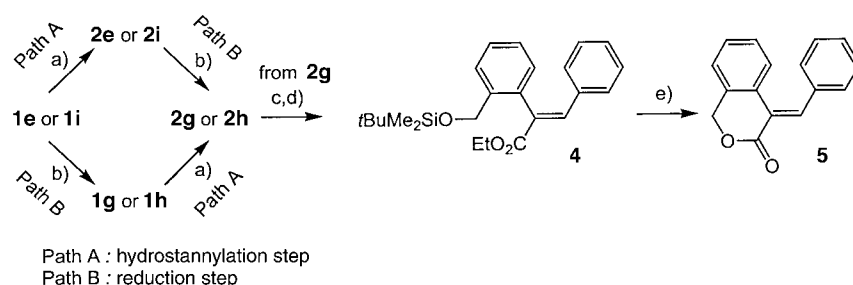
Scheme 1. Synthesis of tricycle 5. Reagents and conditions: a) Bu$_3$SnH (1.1 equiv), [PdCl$_2$(PPh$_3$)$_2$] (1 %), THF, 20 °C, 30 min (2e: 95 %, 2i: 90 %, 2g: 95 %, 2h: 81 %); b) NaBH$_4$, MeOH, −20 °C (1g: 74 %, 1h: 70 %, 2g: 67 %, 2h: 78 %); c) tBuMe$_2$SiCl (1.2 equiv), imidazole, DMF, 20 °C, 80 %; d) 1) nBuLi (1.1 equiv), THF, −40 °C, 0.5 h; 2) (EtO)$_2$CO, THF, −78 °C →20 °C, 1 h, 57 %; e) nBu$_4$NF (1.2 equiv), THF, 0° →20 °C, 60 %.

Table 3. Comparative chemical shifts (^{13}C NMR) of C≡C in *ortho*- and *para*-substituted diaryl alkynes **1**.

Entry		Ratio[a] **2α:2β**	^{13}C shifts[b] (±0.05 ppm)		$\Delta\delta_{C\beta\text{-}C\alpha}$
			δC_α	δC_β	
1	**1s**: R = *p*-Me	50:50	89.6	88.7	−0.9
2	**1o**: R = *o*-Me	93:7	88.6	93.6	5.0
3	**1r**: R = *p*-OMe	(40:60)[c]	89.4	88.1	−1.3
4	**1m**: R = *o*-OMe	90:10	85.7	93.4	7.7
5	**1d**: R = *p*-CH$_2$OH	50:50	89.7	89.4	−0.3
6	**1g**: R = *o*-CH$_2$OH	100:0	86.7	94.0	7.3
7	**1c**: R = *p*-CO$_2$Et	75:25	88.6	92.2	3.6
8	**1f**: R = *o*-CO$_2$Et	100:0	88.2	94.1	5.9
9	**1b**: R = *p*-CHO	85:15	88.5	93.3	4.8
10	**1e**: R = *o*-CHO	100:0	84.9	96.3	11.4

[a] Ratios were determined by ^{1}H NMR spectra of the crude reaction mixture. [b] Shifts are relative to external CDCl$_3$. The assignment of the ^{13}C NMR chemical shifts of the triple bond was established by HMBC and HSQC NMR spectroscopy. [c] Interchangeable ratio.

1e and **1f**, in comparison to the *para* derivatives (**1b** and **1c**), showed that the presence of an *ortho* π-electron-withdrawing group induces strong electronic polarization of the carbon–carbon triple bond, which makes the C$_\beta$ atom more electron positive and the C$_\alpha$ atom more electron negative (i.e. the signal arising from the C$_\beta$ atom is 3.0 ppm upfield and the signal from the C$_\alpha$ atom is 3.6 ppm downfield when **1b** and **1e** are compared). More interestingly, for alkynes **1g**, **1m**, and **1o** in comparison with the *para* derivatives (**1d**, **1r**, and **1s**), the presence of an *ortho* σ-electron-donating group induced an inversion of the polarization of the carbon–carbon triple bond (the C$_\alpha$ atom becomes more electron rich than the C$_\beta$ atom). This is illustrated by the change of sign of $\Delta\delta_{C\beta\text{-}C\alpha}$ values in *ortho*-substituted alkynes, which becomes positive rather than negative in the *para* derivatives. In Table 3, the presence of a methyl substituent in the *ortho* position increases the difference in the ^{13}C NMR chemical shift of the signals arising from the $\Delta\delta_{C\beta\text{-}C\alpha}$ atom from −0.9 ppm (for the $\Delta\delta_C$ atom of the *para*-substituted aryl alkyne **1s**) to 5.0 ppm (**1o**; entries 1 and 2, Table 3). A similar situation was noted when comparing various *ortho*- and *para*-substituted diaryl alkynes **1** (Table 3). We believe that this electronic polarization may be responsible for the remarkable regioselectivity observed, and therefore the hydride (H-PdSnBu$_3$) preferentially adds to the more electron-deficient terminus of the alkyne. To our knowledge, this reflection of the electronic effect of *ortho* substituents across the triple bond in the ^{13}C NMR spectra has never been reported.

In summary, we have demonstrated, for the first time, that a wide variety of unsymmetrical diaryl alkynes can undergo regioselective hydrostannylation when the diaryl alkyne is *ortho* substituted, regardless of the electronic nature of the substituent. Additionally, we showed for the first time that this *ortho* substituent induced dramatic electronic polarization of the carbon–carbon triple bond of the diaryl alkyne, which was presumably responsible for the α regioselectivity observed. The synthetic methodology described not only provides an easy access to stannylated-stilbene derivatives that are not easily prepared by other routes, but also will open up significant possibilities for performing various regioselective hydro- and carbo-metallation reactions of unsymmetrical diaryl (or heteroaryl) alkynes.

Experimental Section

[1] For a recent review on metal-catalyzed hydrostannylations, see: a) N. D. Smith, J. Mancuso, M. Lautens, *Chem. Rev.* **2000**, *100*, 3257–3282; b) H. X. Zhang, F. Guibé, G. Balavoine, *Tetrahedron Lett.* **1988**, *29*, 619–622; c) H. X. Zhang, F. Guibé, G. Balavoine, *J. Org. Chem.* **1990**, *55*, 1857–1867.

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[5] F. Liron, P. Le Garrec, M. Alami, *Synlett* **1999**, 246–248.

[6] Under radical conditions (azobisisobutyronitrile, 80°C), hydrostannylation of **1g** gave a mixture of all four regio- and stereoisomers in 52% yield.

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[9] M. Alami, F. Ferri, G. Linstrumelle, *Tetrahedron Lett.* **1993**, *34*, 6403–6406.

[10] Performing the hydrostannylation of diaryl alkyne **1r** (see Table 3) with a methoxy group in the *para* position of the phenyl group produced a 40:60 mixture of geometric isomers.

[11] The ^{13}C NMR chemical shifts are proportional to the electron density of carbon, see: D. J. Sardella, *J. Am. Chem. Soc.* **1973**, *95*, 3809–3811.