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

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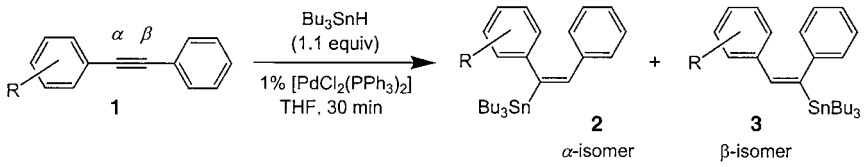
It is well known that the palladium-catalyzed hydrostannylation of internal alkynes proceeds in a stereoselective manner (*cis* addition) to yield vinyl stannanes.[1] Regiochemical control of this reaction, nevertheless, remains a challenge, especially in the case of unsymmetrical disubstituted alkynes. 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_3SnH 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_2OH, 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_3Sn group being α relative to the *ortho*-substituted aryl moiety, selectivity $\alpha:\beta = 100:0$, entries 5, 6, and 7). Stereoisomers **3e–g** were not detected by ^1H 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 chelation 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, $\alpha:\beta$ 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_3SnH. Thus, hydrostannylation of **1o**, which bears an *ortho* methyl substituent, resulted mainly in

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_2Et		81[b]
4	**d**: *p*-CH_2OH		86[b]
5	**e**: *o*-CHO	95	–[a]
6	**f**: *o*-CO_2Et	81	–[a]
7	**g**: *o*-CH_2OH	95	–[a]

[a] Stereoisomers **3** were not detected by ^1H 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 ^1H NMR spectra in the crude reaction mixture.

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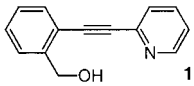
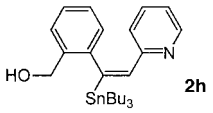
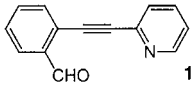
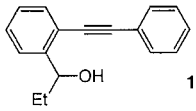
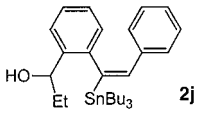
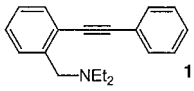
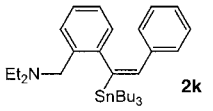
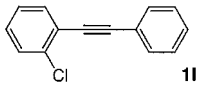
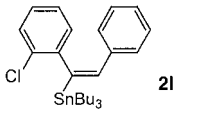
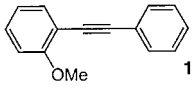
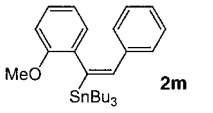
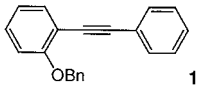
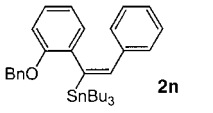
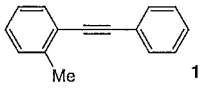
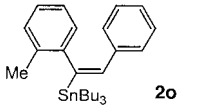
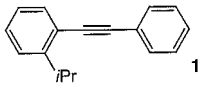
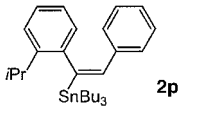
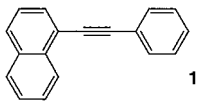
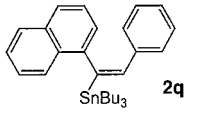
Table 2. Synthesis of various stannylated stilbene derivatives and related compounds.[a]

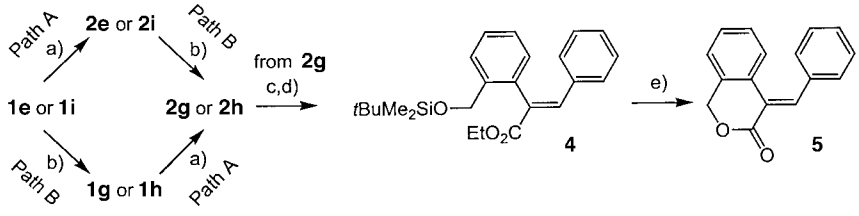
Entry	Diaryl alkyne[b] **1**	Vinyl stannane[c] **2**	Yield[d] [%]
1	 **1h**	 **2h**	81
2	 **1i**	 **2i**	90
3	 **1j**	 **2j**	91
4	 **1k**	 **2k**	60
5	 **1l**	 **2l**	85
6	 **1m**	 **2m**	94[e]
7	 **1n**	 **2n**	81
8	 **1o**	 **2o**	91[e]
9	 **1p**	 **2p**	76
10	 **1q**	 **2q**	67

[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_2Cl_2 followed by amination[7] (Et_2NH, K_2CO_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 = *i*Pr, 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_3SnH 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_α 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_3SnH (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) *t*$BuMe_2SiCl$ (1.2 equiv), imidazole, DMF, 20 °C, 80%; d) 1) *n*BuLi (1.1 equiv), THF, −40 °C, 0.5 h; 2) $(EtO)_2CO$, THF, −78 °C → 20 °C, 1 h, 57%; e) *n*Bu_4NF (1.2 equiv), THF, 0° → 20 °C, 60%.

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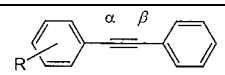
Table 3. Comparative chemical shifts (^{13}C NMR) of C≡C in *ortho*- and *para*-substituted diaryl alkynes **1**.

Entry		Ratio[a] ***2α*:*2β***	^{13}C shifts[b] (±0.05 ppm) δC_α	δC_β	$\Delta\delta_{C\beta\text{-}C\alpha}$
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_2OH	50:50	89.7	89.4	−0.3
6	**1g:** R = *o*-CH_2OH	100:0	86.7	94.0	7.3
7	**1c:** R = *p*-CO_2Et	75:25	88.6	92.2	3.6
8	**1f:** R = *o*-CO_2Et	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_β atom more electron positive and the C_α atom more electron negative (i.e. the signal arising from the C_β atom is 3.0 ppm upfield and the signal from the C_α 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_α atom becomes more electron rich than the C_β 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

2g: Tributyltin hydride (11 mmol, 2.95 mL) was added dropwise at room temperature to a solution of [$PdCl_2(PPh_3)_2$] (0.1 mmol, 71 mg) and alkyne **1g** (10 mmol, 2.08 g) in THF (15 mL). The dark brown reaction mixture was stirred for an additional 15 min and then concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether:AcOEt 80:20 gave 4.74 g (95%) of pure **2g**. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.31 (d, 1H, J = 7.6 Hz), 7.19 to 6.84 (m, 8H), 6.63 (s, 1H, $J_{H\text{-}Sn}$ = 65 Hz), 1.47 to 1.11 (m, 13H), 0.96 to 0.71 (m, 15H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 148.7, 143.6, 138.9, 137.1, 134.9, 128.6, 128.2, 127.9, 127.8, 127.1, 126.0, 125.6, 63.2, 28.2, 27.3, 13.6, 10.2.

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