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Cis-Trans Stereoselectivity in the Stannylmetallation of Diphenylacetylene

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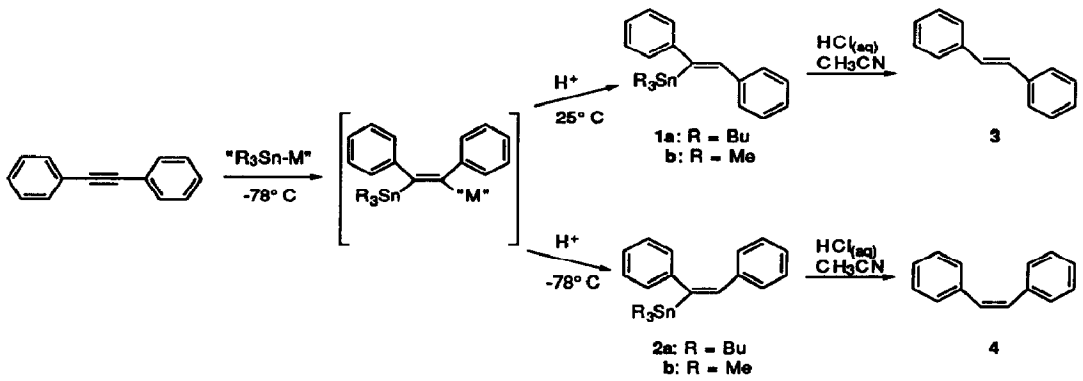
Abstract: Stereospecific *cis*- or *trans*- stannylcupration of diphenylacetylene can be obtained by temperature control during vinylcuprate hydrolysis.

Of the many compounds that have been screened for binding affinity to the estrogen receptor, one of the most promising non-steroidal classes is the triarylolefins,[1] which includes Tamoxifen and Clomiphene. We envisioned a stereoselective synthetic approach to these compounds, which would rely upon the stannylmetallation of a diarylacetylene followed by the introduction of the third aryl group *via* palladium-catalyzed coupling with an aryl iodide. The stannylmetallation of diarylalkynes has been reported,[2,3] and the coupling of aryl halides with metalloalkenes is also known.[4-8]

Our initial investigation into this chemistry was immediately rewarded with an unexpected and intriguing result. When diphenylacetylene was treated with a higher-order tributylstannylcuprate at -78 °C and the reaction quenched at this temperature by the addition of methanol, we obtained an inseparable 2:3 mixture of vinylstannanes **1a** ($^3J_{SnH}$ = 118 Hz) and **2a** ($^3J_{SnH}$ = 50 Hz), respectively (Scheme 1). The formation of *trans*-stannylmetallation product **1a** is unprecedented, and we hypothesized that the addition of ambient temperature methanol raised the reaction temperature sufficiently to allow formation of the *trans*-addition product during protonation.[9] That this was the case was verified by performing two parallel experiments. In the first, the stannylcupration was conducted at -78 °C in the presence of excess methanol (kinetic conditions), and only the *cis*-addition product **2a** was observed. In the second experiment, the reaction mixture was allowed to warm to room temperature before the methanol quench, and in this case only the *trans*-addition product **1a** was detected. We have found that vinylstannanes **1a** and **2a**, which are configurationally stable over several months, undergo stereospecific protodestannylation with retention of olefin geometry to *trans*- and *cis*-stilbene (**3** and **4**), respectively.



Scheme 1. Stannylcupration of diphenylacetylene.

Many of our triarylolefinic targets contain a *trans*-1,2-diphenylethene backbone. Because we had assumed, based on literature precedent, that stannylmetallation would afford the product of *cis*-addition, our long-range synthetic plans involved the stannylmetallation of 1-aryl-2-phenylalkynes with subsequent phenylation of a metallo-alkene intermediate. The success of this approach would rely in large part on the regioselectivity of the stannylmetallation. The discovery of *trans*-stannylcupration methodology obviates the issue of regiochemistry for these substrates, and as such stereochemistry became a primary arbiter in our search for the most useful stannylmetallation process. Specifically, we examined a number of reagents[3,10-12] for both their propensity to effect the stannylmetallation of diphenylacetylene and their ability to provide *trans*-addition products. The results of this study are summarized in Table 1.

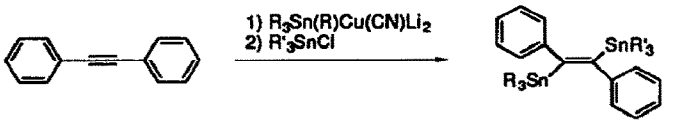
Table 1. Stannylmetallation of Diphenylacetylene.

Entry	Stannylmetallation Reagent	Product(s)	% Yield
1	$Bu_3Sn(Bu)Cu(CN)Li_2$[a]	**1a**	61
2	$Bu_3Sn(Bu)Cu(CN)Li_2$[b]	**2a**	39
3	$Me_3Sn(Me)Cu(CN)Li_2$[a]	**1b**	84
4	$Me_3Sn(Me)Cu(CN)Li_2$[b]	SM[c]	88
5	$(R_3Sn)_2Zn$[a]	SM[c]	d
6	$Bu_3Sn(9\text{-}BBN)$[a]	**1a + 2a**	5
7	$Bu_3SnMgMe$[a]	**1a**	61
8	$Bu_3SnAlEt_2$[a]	**2a**	37

[a] Thermodynamic conditions.
[b] Kinetic conditions.
[c] Starting material (diphenylacetylene).
[d] Yield not determined.

Based upon the results presented above, stannylmagnesiation and stannylcupration were selected as the methods of choice for preparation of the initial 1,2-dimetallo-1,2-diphenylethene. However, we were also interested in preparing one other class of 1,2-dimetallo-1,2-diphenylethenes, namely 1,2-bis(trialkylstannyl)-

alkenes. For steric reasons, these compounds cannot be prepared by addition of ditin reagents to diphenylactylene.[13] However, stannylcupration (thermodynamic conditions) followed by quenching with the appropriate trialkyltin chloride readily provides the target compounds **5a-c** (Scheme 2). The choice of reagents for the symmetrical **5a** and **5b** is obvious; **5c** was made from a trimethylstannylcuprate and tributyltin chloride. When this chemistry was performed under kinetic conditions followed by workup at ambient temperature, the only product isolated was **2a**. These results suggest that, while the desired *cis*-bis(stannane) was formed, it underwent mono-protodestannylation during workup.

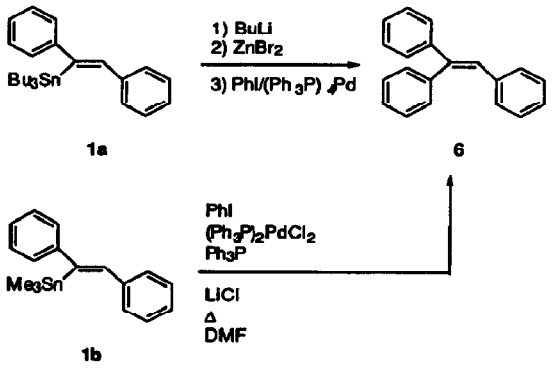


5a: R = R' = Bu
b: R = R' = Me
c: R = Me, R' = B

Scheme 2. Preparation of 1,2-bis(trialkylstannyl)alkenes.

We began our aryl coupling study with the initial adducts of stannylmetallation, the *cis*-1,2-diphenyl-1-trialkylstannyl-2-metalloethenes, using iodobenzene as the coupling partner. Except for the vinyl magnesium reagent, where a nickel catalyst was employed, a palladium (0) or palladium (II) catalyst was used for all of the couplings. The *trans*-vinylcuprate and *trans*-vinyl Grignard were obtained directly by stannylmetallation of diphenylacetylene. The *trans*-vinylborane and *trans*-vinylalane were prepared by transmetallation of the vinylcuprate obtained under thermodynamic conditions. Finally, the treatment of bis(stannane) **5b** with butyllithium followed by transmetallation with zinc bromide provided the vinylzinc. It should be noted that these organometallics were not characterized but were used immediately after preparation. Unfortunately, none of these coupling reactions provided any triarylvinylstannane, even under forcing conditions, and despite the examination of a number of catalysts. In every case but one, the only isolated products were **1a** or **1b**. The Grignard reaction was the exception, providing tributylstannylbenzene in 80% yield, presumably by coupling of the starting organometallic with iodobenzene. This observation provides additional evidence[14,15] that the stannylmetallation is reversible, since in the absence of haloarene vinylstannane **1a** was the major product (Table I, Entry 7). That the failure of these couplings is a steric phenomenon is supported by our one success in this area: when vinylstannane **1a** was treated with butyllithium, followed by transmetallation with zinc bromide, the resulting vinylzinc coupled nicely with iodobenzene to afford triphenylethylene **6** in 67% yield (Scheme 3). It seems unlikely that the fact that the only successful coupling involved a disubstituted metalloalkene was a coincidence. With respect to the coupling of isolated vinylstannanes, we studied both the mono-stannylalkenes **1a** and **1b**, as well as the bis(stannanes) **5a-c**. Once again, the coupling partner was iodobenzene, and several reported Stille coupling conditions were examined using both palladium (0) and palladium (II) catalysts. Our results here parallel those described above in that in every case except one, starting vinylstannane was recovered from the reaction mixture. And once again, the only successful coupling involved the least sterically congested system:

monotrimethylstannylstilbene **1b** afforded triphenylethylene **6** in 35% yield under catalysis by bis-(triphenylphosphine)palladium (II) chloride in dimethylformamide (Scheme 3).



Scheme 3. Metalloalkene-aryl iodide coupling.

We have found that stannylmetallation of diphenylacetylene provides a useful route to trialkylstannylstilbenes. In particular, stannylcupration has been found to offer unanticipated selectivity in terms of product stereochemistry, affording either *cis*- or *trans*-addition to the alkyne, depending upon reaction conditions. The *trans*-addition mode is particularly attractive, since it provides products which are difficult to prepare by existing methods. If the stannylmetallation is quenched with a tin chloride, 1,2-bis(trialkylstannyl)stilbenes are obtained. We are continuing to examine and extend this chemistry as we apply it to the synthesis of specific bioactive targets.

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