

Synthesis of Tetrasubstituted Alkenes by Stereo- and Regioselective Stannyllithiation of Diarylacetylenes

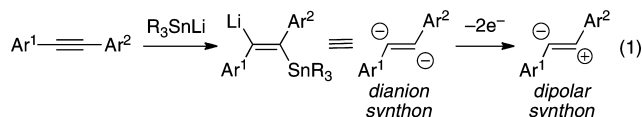
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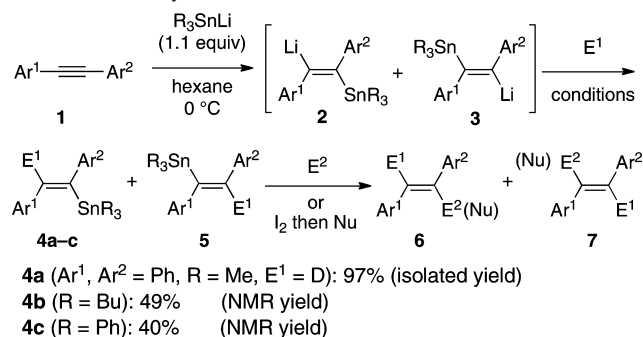
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Abstract: Addition of trimethylstannyllithium to a diarylacetylene takes place exclusively in an anti-fashion to produce a lithio vinylstannane intermediate. The regioselectivity of the addition is controlled by the steric and electronic property of the acetylene and reaches up to >99:1. The two newly formed C–metal bonds can be sequentially and stereospecifically transformed into two new C–C bonds as illustrated by stereoselective synthesis of 4-hydroxytamoxifen and its regioisomer. A tetraarylethene bearing different aryl groups can be synthesized similarly and cyclized to a substituted dibenzo[*g,p*]chrysene derivative via a palladium-catalyzed arylation reaction.

The chemistry of tetrasubstituted alkenes has been underrated because of the paucity of synthetic access.¹ Providing a potential route to such alkenes by way of a dianion or dipolar synthon, the addition of a bimetallic species to an internal acetylene is intriguing (eq 1) but to date has not received proper attention because of selectivity problems, in particular regioselectivity.² We report herein that the stannyllithiation of a simple diarylacetylene **1** proceeds with 100% anti-selectivity to generate the *Z* dimetallic product **2** or **3**³ and that the resulting C–Li and C–Sn bonds can be converted sequentially to two C–C bonds, to selectively produce tetrasubstituted alkenes possessing various functional groups (Scheme 1). The regioselectivity of the addition is sensitive to the steric and electronic nature of the two aryl groups and may reach 90–99% (Table 1), which is rather remarkable in light of some previously reported examples.^{4,5} Notably, the present reaction also provides a stereoselective entry to 1,1,2,2-tetraarylethenes and chrysene derivatives (Scheme 3).



Scheme 1. Stannyllithiation Route to Tetrasubstituted Alkenes^a



^a Conditions. *a*: E¹ (1.1 equiv), hexane, 0 °C to rt; *b*: ZnCl₂ (1.1 equiv), hexane/THF = 2/1, 0 °C to rt, then E¹ (1.1 equiv), Pd₂(dba)₃·CHCl₃ (5 mol %), SPhos (20 mol %), rt.

Table 1. Synthesis of 1,2,2-Triorgano Stannyllalkenes **4** and **5**

Entry	Ar ¹	Ar ²	E ¹ (condition)	Isolated yield/% (4:5 ratio) ^a
1	Ph	Ph	EtI (<i>a</i>)	82 (–)
2	Ph	Ph	CH ₂ =CHCH ₂ Br (<i>a</i>)	62 (–)
3	Ph	Ph	PhCHO (<i>a</i>)	80 (–)
4	Ph	Ph	Ph ₂ CO (<i>a</i>)	88 (–)
5	Ph	Ph	<i>p</i> -MeO–C ₆ H ₄ –I (<i>b</i>)	91 (–)
6	Ph	Ph	3-pyridyl–I (<i>b</i>)	76 (–)
7	Ph	<i>o</i> -Tol ^b	<i>p</i> -MeO–C ₆ H ₄ –I (<i>b</i>)	86 (14:86)
8	Ph	<i>o</i> -MeO–C ₆ H ₄	<i>p</i> -Tol–I (<i>b</i>) ^b	87 (10:90)
9	Ph	1-naphthyl	<i>p</i> -MeO–C ₆ H ₄ –I (<i>b</i>)	75 (1:>99)
10	Ph	<i>p</i> -MeO–C ₆ H ₄	<i>p</i> -Tol–I (<i>b</i>) ^b	84 (91:9)
11	Ph	<i>p</i> -F–C ₆ H ₄	<i>p</i> -MeO–C ₆ H ₄ –I (<i>b</i>)	80 (34:66)
12	Ph	<i>p</i> -Cl–C ₆ H ₄	<i>p</i> -MeO–C ₆ H ₄ –I (<i>b</i>)	74 (36:64)
13	<i>o</i> -Tol ^b	<i>p</i> -MeO–C ₆ H ₄	<i>p</i> -Tol–I (<i>b</i>) ^b	85 (>99:1)
14	<i>o</i> -Tol ^b	<i>p</i> -MeO–C ₆ H ₄	<i>p</i> -CF ₃ –C ₆ H ₄ –I (<i>b</i>)	84 (>99:1)
15	<i>o</i> -Tol ^b	<i>p</i> -MeO–C ₆ H ₄	2-thienyl–I (<i>b</i>)	81 (>99:1)

^a Determined from the ¹H NMR of isolated isomer mixture. ^b Tol = tolyl.

According to a report in 1981, triethylstannyllithium in THF adds to diphenylacetylene in only 2% yield,^{6,7} and in our case, trimethylstannyllithium in THF afforded the *Z*-adduct **2** in 31% yield. To our pleasant surprise, trimethylstannyllithium in hexane at 0 °C afforded after D₂O quenching (2-deuterio-1,2-diphenylethynyl)stannane **4a** in 97% yield with 100% *Z* selectivity (for all cases shown in Table 1) and with 100% deuterium incorporation. The reaction of tributyl- and triphenylstannyllithium took place similarly but in lower yield (Scheme 1). Although this reaction can be applied only to diarylacetylenes, it exhibits considerable synthetic utility because of the versatility of the lithiated vinylstannane intermediate and the regio- and stereoselectivity of the reaction.

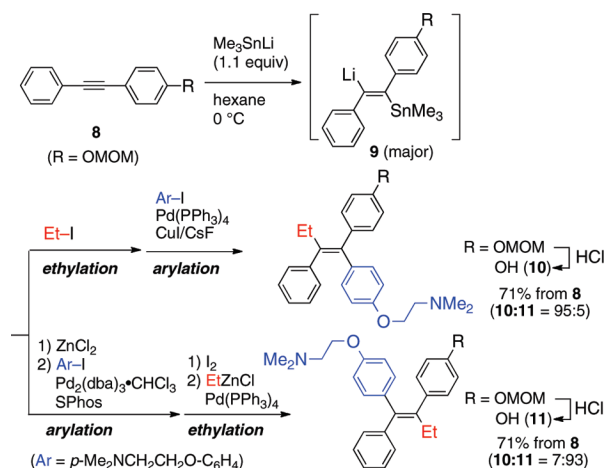
We can trap the lithio intermediate **2** or **3** with a variety of electrophiles to obtain 1,2,2-triorgano stannyllalkenes (Scheme 1 and Table 1; condition *a*; no catalyst). Trapping with ethyl iodide and allyl bromide afforded the 2-ethylated and 2-allylated 1-stannyethene in 82% and 62% isolated yield, respectively (entries 1 and 2).⁸ The reaction with benzaldehyde and benzophenone afforded the corresponding secondary and tertiary allylic alcohols in 80% and 88% yield, respectively (entries 3 and 4). After transmetalation from lithium to zinc, Negishi coupling (condition *b*, with SPhos⁹ ligand) with *p*-anisyl and 3-pyridyl iodides afforded 2-(*p*-anisyl)- and 2-(3-pyridyl)-1-stannyllalkene in 91% and 76% yield, respectively (entries 5 and 6). The stannyl group remained intact during these transformations.

The regioselectivity of the stannyllithiation is critically important for this reaction to be synthetically useful and was found to be controlled by subtle steric and electronic effects (entries 7–15). Steric hindrance caused by *o*-tolyl and *o*-anisyl groups puts the stannyl group away from these groups and gave predominantly isomer **5** (14:86 and 10:90, respectively) after trapping with an aryl iodide under condition *b* (entries 7 and 8). The bulkier 1-naphthyl group increased the regioselectivity to >99% (entry 9).

Interestingly, the electronic properties of Ar¹ and Ar² control the regioselectivity. An electron-rich aryl group places the stannyl group

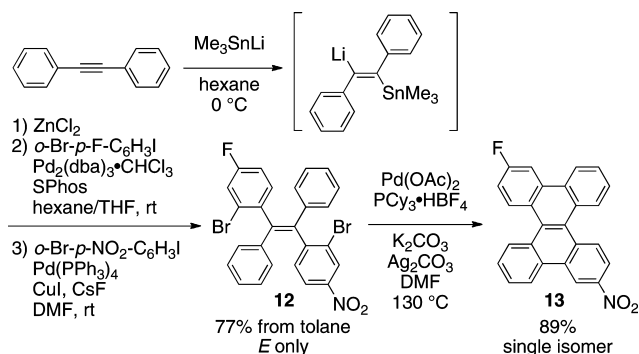
onto the same carbon to which this aryl group is attached (entry 10 as opposed to entry 8 where the steric effect of the *o*-anisyl group wins); on the other hand, an electron-withdrawing aryl group puts the stannyl group away from this aryl group (entries 11 and 12). With an added steric factor ($\text{Ar}^1 = o\text{-Tol}$), the selectivity increases to >99:1 (entries 13–15). This electronic effect can be understood in terms of the stabilization by the lithium atom of an anionic charge on the vinylic carbon atom that develops during the course of the reaction.¹⁰ However, the reaction time was found to be insensitive to the electronic properties of the *p*-substituent (entries 10–12), suggesting that the rate-limiting step differs from the regioselectivity-determining step.

Scheme 2. Selective Synthesis of Two Regioisomers of Hydroxytamoxifen



We illustrate the synthetic utility of the reaction by a 1-g scale synthesis of two different regioisomers, 4-hydroxytamoxifen **10** and 4'-hydroxytamoxifen **11** from the readily available compound **8** (Scheme 2). To obtain **10**, the stannylolithiation of **8** generated the vinylolithium intermediate **9**, which was trapped in situ by EtI, and the ethylated product was arylated with *p*-Me₂NCH₂CH₂O-C₆H₄-I.¹¹ Removal of the methoxymethyl (MOM) group gave **10** in 71% overall yield in a **10:11** ratio of 95:5. To obtain the regioisomer **11**, we introduced the *p*-Me₂NCH₂CH₂O-C₆H₄ group first. Thus, we transmetalated the vinylolithium intermediate **9** into the corresponding zinc reagent and coupled it with the required aryl iodide. The vinylstannane product was then converted to the corresponding iodide and coupled with ethylzinc chloride under palladium catalysis. Removal of the MOM group gave **11** in 71% overall yield in a **10:11** ratio of 7:93.

Scheme 3. Stereoselective Synthesis of a Dibenzo[*g,p*]chrysene Derivative



Second, we show a selective synthesis of an unsymmetrically substituted dibenzo[*g,p*]chrysene derivative (Scheme 3).¹² Diphenyl-

acetylene was stannylolithiated and then successively treated with 2-bromo-4-fluoro-1-iodobenzene and 2-bromo-1-iodo-4-nitrobenzene to afford the tetraarylethene **12** in 77% yield with 100% stereoselectivity (see Supporting Information). Palladium-catalyzed cyclization¹³ of **12** gave the dibenzochrysene derivative **13** in 89% yield.

In summary, we have developed the stannylolithiation of diarylacetylene, which proceeds in a 100% anti-addition fashion with a regioselectivity up to >99:1, without the assistance of a catalyst or a directing group. This reaction provides a versatile stereo- and regioselective synthesis of multisubstituted alkenes via a dianion or dipolar alkene synthon. Although the origin of the selectivity of the metallometallation step is unclear at this time,¹⁰ the new method complements the previous syntheses of this class of alkenes,¹ such as the reaction of 1,1-dihaloalkene¹⁴ and alkynylmetal species.^{15,16} The method also provides a stereo- and regioselective synthesis of substituted dibenzo[*g,p*]chrysenes that are expected to have good potential as organic semiconductor materials.¹⁷ This dibenzochrysene synthesis is complementary to the previously reported methods that can only be applied to the synthesis of electron-rich derivatives.¹⁸

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Supporting Information Available: Detailed experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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