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On The Stille Vinylation Reactions With α-Styryltrimethyltin

Shu-Hui Chen

Vion Pharmaceuticals Inc., Four Science Park, New Haven, CT 06511, USA

Abstract: Stille vinylation reactions involving α-styryltrimethyltin ***3b*** *and a series of chloro- or bromo-pyridine derivatives are described. In contrast to the rare cine seletivity observed with iodobenzene* ***10a*** *or 3-iodotoluene* ***10b****, reactions between vinyltin* ***3b*** *and a series of 2-halopyridine derivatives* ***15(a-d)*** *yield 1,1-disubstituted ipso-coupled olefins* ***16(a-d)*** *as the predominant products.* © 1997 Elsevier Science Ltd.

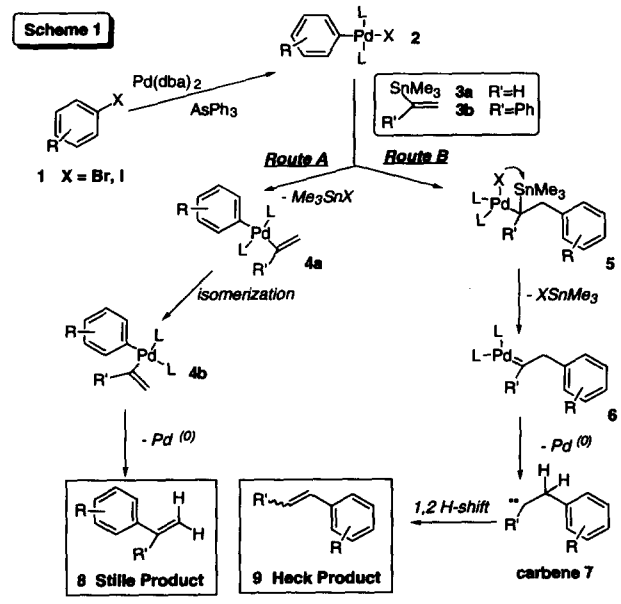
The past decade has witnessed the growing popularity of the usage of palladium-catalyzed cross-coupling reactions for the chemoselective and stereospecific construction of carbon-carbon bonds.[1] In particular, methods that employ vinylstannanes (Stille vinylation) are among the most valuable[2] not only because of their compatibility with most functional groups but also the mildness of the reaction conditions. Mechanistically, it is broadly accepted that Stille vinylation involving vinylstannanes (e.g. **3a**) proceeds through a sequence consisting of oxidative addition, transmetallation, *trans-cis* isomerization and reductive elimination to form 1,1-disubstituted Stille (ipso) product **8** as shown in *Route A* (Scheme 1).[1]

Interestingly, a 1986 report from Kikukawa *et al.* disclosed the unusual cine selectivity observed in the Stille coupling of α-styryltin **3b** with a number of aryl diazonium salts.[3] In this case, the 1,2-disubstituted (cine) products (e.g. **9**) were isolated. Ten years later, a report from Farina *et al.* provided the convincing mechanistic rationale for this interesting cine selectivity by using an elegantly designed crossover experiment.[4] On the basis of these studies, the Stille vinylation with α-styryltin **3b** probably proceeds according to the mechanism depicted in *Route B* (Scheme 1), which features the formation of Pd(0) carbene intermediate **6** *via* α-elimination of Me_3SnX[5] from the carbopalladation adduct **5** followed by an intramolecular 1,2-hydrogen shift[5] providing the Heck-like cine product **9** from carbene **7**.

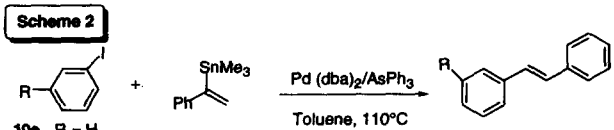
To verify the cine selectivity, α-styryltin **3b**[6] was reacted with iodobenzene **10a** and 3-iodotoluene **10b** under standard Stille coupling conditions as outlined in Scheme 2. Indeed, the *cine* product **11a**[7] or **11b** was isolated in each case as the predominant product. The low yield obtained with iodobenzene is probably due to its poor reactivity under these coupling conditions. Having confirmed the cine selectivity with **10(a,b)**, further study was initiated with the aim of investigating the occurance of this rare cine-substitution in Stille vinylation reactions involving α-styryltin **3b** and a series of halogenated pyridines derivatives shown in Scheme 3.

All reactions outlined in Scheme 3 were performed in a toluene solution containing 1 : 1 molar ratio of halopyridine and vinyltin **3b** along with 0.03 eq. $Pd(dba)_2$ and 0.12 eq. $AsPh_3$ at reflux for 48 hours. As shown in Table 1, the reaction of α-styryltin **3b** with 3-bromopyridine **12a** yielded the *cine*-isomer **14a** as the major product (39%) together with

Scheme 1



Scheme 2

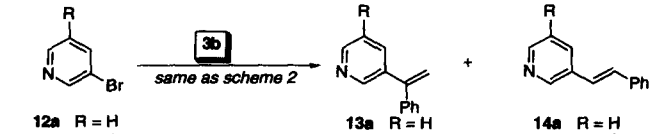


10a R = H
10b R = Me

3b

11a R = H (low yield)
11b R = Me (47%)

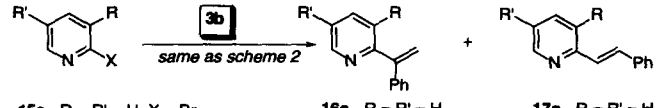
Scheme 3 *Stille Vinylation of Substituted Pyridine Derivatives*



12a R = H
12b R = CO_2Me

13a R = H
13b R = CO_2Me

14a R = H
14b R = CO_2Me



15a R = R' = H, X = Br
15b R = CO_2Me, R' = H, X = Cl
15c R = NO_2, R' = H, X = Cl
15d R = R' = NO_2, X = Cl

16a R = R' = H
16b R = CO_2Me, R' = H
16c R = NO_2, R' = H
16d R = R' = NO_2

17a R = R' = H
17b R = CO_2Me, R' = H
17c R = NO_2, R' = H
17d R = R' = NO_2

Table 1: Product distribution of the Stille vinylation with α-styryltrimethyltin (**3b**):

Entry	*S.M.*	*Reaction Mixture*		*Composition*	*ipso/cine*
		ipso-prod. [a,b]	*cine-prod.* [a,b]	*recov. S.M.*	*ratio*
1	**12a**	**13a** (12.9%)	**14a** (38.7%)	n.a.[c]	1 : 3
2	**12b**	**13b** (13.0%)	**14b** (24.0%)	13%	~1 : 2
3	**15a**	**16a** (6.7%)	**17a** (~0%)	n.a.[c]	>20 : 1
4	**15b**	**16b** (37.0%)	**17b** (4.2%)	22.7%	9 : 1
5	**15c**	**16c** (81.9%)	**17c** (4.4%)	n.d.[d]	19 : 1
6	**15d**	**16d** (64%)	**17d** (~0%)	n.d.[d]	>20 : 1

Note: (a) isolated yields; (b) all compounds exhibiting satisfactory MS and ^{1}H NMR; (c) symbol [n.a.] meaning not isolated; and (d) symbol [n.d.] indicating not detected.

the minor *ipso*-product **13a** (13%) in a ratio of 3 : 1 favoring the *cine*-substitution (entry 1). As shown in entry 2, the coupling of **3b** with 3-bromo-5-nicotinic acid methylester (**12b**)[8] again resulted in the formation of a mixture of *ipso*- and *cine*-isomers (**13b** & **14b**) in a ratio of 1 : 2 favoring the latter. A small amount of starting material (**12b**) was also recovered. Based on the results listed in entry 1 & 2 (Table 1), it appears that the presence of the electron-withdrawing substituent (e.g. "N" atom on pyridine ring, methylester group), positioned *meta* to the leaving group (Br in both cases), is responsible for the modest shift of the regioselectivity from exclusive *cine* (see Scheme 2) to coexistence of both *cine* and *ipso*-isomers with the *cine*-adduct being the major product.

Stille vinylation was further studied using halopyridine derivatives **15(a-d)**. The leaving group within this group (either chloride or bromide) is located *ortho* to the nitrogen atom on pyridine ring. In this event the 2-bromopyridine (**15a**) reacted to give exclusively the *ipso*-isomer (**16a**) in very low yields. However, no *cine*-isomer (**17a**) was isolated (entry 3). Reaction of 2-chloro-3-nicotinic acid methylester (**15b**)[8] with **3b** yielded both the *ipso*-and *cine*-isomers (**16b** & **17b**) with a ratio of 9 : 1 favoring the *ipso*-substitution (entry 4). When 2-chloro-3-nitropyridine (**15c**) was employed as the substrate, the *ipso*-adduct (**16c**) was again isolated as the major product (82% yield), while the *cine*-adduct (**17c**) was minimal (4.4% yield, entry 5). In entry 6, 2-chloro-3,5-dinitropyridine (**15d**) reacted with α-styryltin (**3b**) to afford only the *ipso*-adduct (**16d**) in 64% yield. No cine-adduct (**17d**) was detected. Thus, it became apparent that placing an electron-withdrawing pyridine ring "N" atom *ortho* to the halide moiety (Cl or Br), alone or in conjuction with the presence of additional electron-withdrawing group (e.g. ester, nitro), could steer the *cine/ipso* selectivity towards the latter with a ratio ranging from 9 : 1 to > 20 : 1.

When 4-bromopyridine was used as the substrate, no expected cross-coupling product was detected. It should also be mentioned that the by-product derived from homo-coupling of **3b** was produced (less than 10%) in almost every reaction listed in Table 1. Stille vinylation proceeded faster with substrates **15 (a-d)** than with **12(a,b)**.

Furthermore, comparing the results listed in entry 2 & 4 as well as entry 1 & 3 reveals that the *cine/ipso* selectivity of the Stille vinylation is dictated primarily by the position of the electron-withdrawing groups (EWGs) attached to the arylhalides. Evidently, *ortho*-substituted EWGs can exert a more profound effect than its *meta*-substituted counterparts.

It is worthwhile to mention in this context that both Stork[9] and Crisp[10] reported the effect of attaching EWG(s) to arylhalide on the regioselcectivity in Stille vinylation reactions. In addition, Levin recently reported that the *ipso*-selectivity in Stille vinylation of α–stannyl acrylate was restored by the addition of CuI.[11] However, no detailed study concerning the dependence of regioselectivity on actual positioning of the EWG(s) has been documented. Therefore, the present study will provide useful information to the synthetically valuable Stille vinylation reactions.

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