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Reactions of vinyltributylgermanes and aryl halides under Heck conditions

Nicole M. Torres, Jérôme M. Lavis, Robert E. Maleczka Jr. *

Department of Chemistry, Michigan State University, East Lansing, MI 48824, USA

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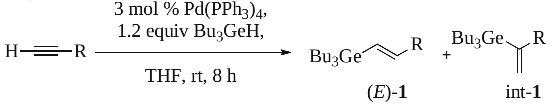
ABSTRACT

We describe the palladium-mediated reaction of vinyltributylgermanes with aryl halides under Heck conditions. Depending on their degree of substitution, (*E*)-vinyltributylgermanes preferentially afford either the cine or *Z*-alkenyl coupled products in moderate yields. Substituents at the allylic position, especially oxygen, impact regio- and stereoselectivity.

In 1990, Ikenaga and Kikukawa announced the palladium-catalyzed aryldegermylation of styryltrimethylgermanes upon reaction with arenediazonium tetrafluoroborates.[1] Six years later, Kosugi reported that while the Pd-mediated coupling of vinyltributylgermane with *p*-bromotoluene afforded *p*-methylstyrene in 60% yield, most reactions of this type did not give cross-coupled products.[2] Chemists awaiting further descriptions of vinylgermane cross-couplings had to wait until 2002 when Oshima showed that aryltri(2-furyl)germanes can be instrumental in Pd-catalyzed biaryl syntheses[3] and Faller expanded the scope and utility of germatranes.[4] More recently, tris(trimethylsilyl)vinylgermanes have found their place as efficient coupling partners upon the basic-oxidative treatment described by Wnuk.[5] Kosugi and Fugami continue to develop germanium coupling chemistry demonstrating that aryl trichlorogermanes,[6] or the hydrolyzed sesquioxide variants,[7] can partake in biaryl couplings in aqueous media. Likewise, Spivey's progress on polymer- or fluorous-tagged germane couplings that are activated by photooxidation opens the door for organogermane use in library synthesis.[8] Prompted by these continuing efforts as well as by new advances in germane syntheses,[9] we decided to communicate our own results on the Pd-mediated reactions of vinyltributylgermanes.

(*E*)-Vinyltributylgermanes used in this study were synthesized by Pd-mediated hydrogermylation of various alkynes.[10] As illustrated in Table 1, the level of regioselectivity exhibited by these reactions was dependent on the extent of substitution at the propargylic position of the starting alkyne. Unhindered alkynes (entries 4–8) gave intrusive amounts of internal (proximal) vinyltributylgermanes.

Table 1
Hydrogermylations



Entry	Alkyne	Product	% Yield	*E*/int[a]
1	2-Methyl-3-butyn-2-ol	**1a**	95	100% *E*
2	1-Ethynyl-cyclohexanol	**1b**	89	100% *E*
3	3-Methyl-1-butyne	**1c**	73	100% *E*
4	Hex-1-yn-6-ol	**1d**	64	4.0/1
5	Pent-1-yn-5-ol	**1e**	75	3.8/1
6	1-Pentyne	**1f**	78	3.6/1
7[b]	Propargyl alcohol	**1g**	81	1.7/1
8	O-THP hex-1-yn-6-ol	**1i**	62	1.3/1
9	O-TBS 2-methyl-3-butyn-2-ol	**1j**	91	100% *E*

[a] Yields and *E*/internal ratios based on isolated material.
[b] Reaction time 14.5 h; *E*/internal ratio determined by ^{1}H NMR analysis of the crude reaction mixture.

Initial cross-coupling experiments under traditional Stille conditions proved interesting in that (*E*)-vinyltributylgermane **1a** solely gave *Z*-product **2**, albeit in a modest 30% yield (Scheme 1). This selective formation of a *Z*-product from an (*E*)-germane was a distinctive feature of our system and therefore worthy of additional study.

We surveyed various reaction conditions with the aim of improving our understanding and efficiency of the process. Focusing first on Stille-type conditions,[11] we examined different Pd (Pd_2dba_3, $Pd(OAc)_2$, and $PdCl_2[P(o\text{-}Tol)_3]_2$), and ligand ($AsPh_3$, TFP, $(o\text{-}Tol)_3P$, and dppe) mixtures. No catalyst–ligand combinations

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* Corresponding author. Tel.: +1 517 355 9715x124; fax: +1 517 353 1793.
E-mail address: maleczka@chemistry.msu.edu (R.E. Maleczka Jr.).

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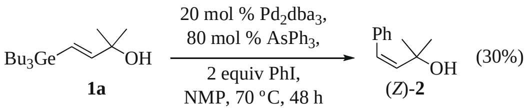
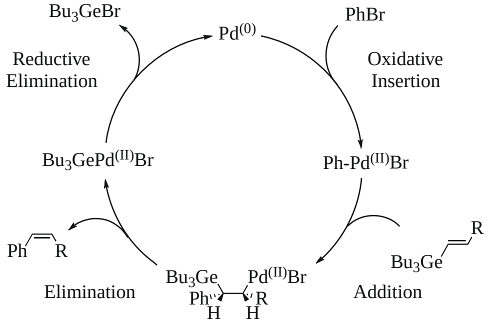


Scheme 1. Initial coupling reaction.

that were studied improved the Scheme 1 results. Furthermore, while repeating the reaction described above in the presence of CuI the reaction failed, providing evidence against a Stille-type mechanism.

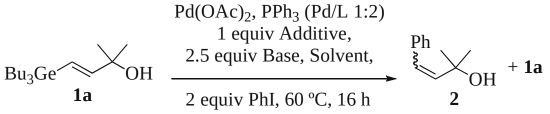
Faller previously suggested a Heck reaction as one possible contributor in the coupling of alkenylgermatranes.[4a,12] We too recognized that formation of (*Z*)-**2** could be explained by a Heck-type mechanism[11,13] involving *syn* β-germyl elimination of the palladium intermediate (Scheme 2). Therefore, we quickly moved to investigate Heck-type catalytic systems.[11,13]

An exploration of Heck-type conditions soon identified $Pd(OAc)_2$ and Ph_3P as a suitable catalyst and ligand, respectively. Experimentation with additives, bases,[14] and solvents[15] (Table 2) revealed that Bu_4NBr and K_2CO_3 in acetonitrile/water were optimal.[16] A reaction temperature of ~70 °C proved best. Couplings tended not to occur at temperatures <50 °C, whereas reactions at much higher than 70 °C gave lower yields, most likely due to catalyst decomposition. After screening catalyst loadings (entries 1 and 7–9) we decided that 20 mol % Pd struck the best balance between stoichiometry and yield. Furthermore, 17–18% biaryl was observed with PhI.[17] Thus the choice Heck conditions to emerge were 2 equiv electrophile, 20 mol % $Pd(OAc)_2$, 40 mol % PPh_3,[18] 1 equiv Bu_4NBr, and 2.5 equiv K_2CO_3 in $MeCN/H_2O$ (9:1) at 70 °C.



Scheme 2. Proposed mechanism.

Table 2
Ligand, additive, base, and solvent screening for the reaction of **1a** under Heck conditions



Entry	Mol % Pd	Additive	Base	Solvent	% **1a**[a]	% Yield[a] (*Z*/*E*/int)
1	10	Bu_4NBr	K_2CO_3	aq MeCN[b]	53	47 (17/4/1)
2	10	Bu_4NHSO_4	K_2CO_3	aq MeCN[b]	21	34
3	10	—	K_2CO_3	aq MeCN[b]	66	34 (21/1/5)
4	10	Bu_4NBr	$NaHCO_3$	aq MeCN[b]	57	43 (17/1/2)
5	10	Bu_4NBr	$NaHCO_3$	DMF	80	6
6	10	Bu_4NBr	Ag_2CO_3	aq MeCN[b]	65	30
7	5	Bu_4NBr	K_2CO_3	aq MeCN[b]	54	46 (17/5/1)
8	20	Bu_4NBr	K_2CO_3	aq MeCN[b]	45	55 (10/3/1)
9	50	Bu_4NBr	K_2CO_3	aq MeCN[b]	63	37 (4/1/0)

[a] Yields of **2** and unreacted **1a** as well as *Z*/*E*/internal ratios were determined by ^1H NMR analysis of crude reactions with MeOH, mesitylene, or TMS-O-TMS as an internal standard.
[b] $MeCN/H_2O$ (9:1).

Although the Heck conditions appeared superior to the Stille conditions shown in Scheme 1, we thought it prudent to compare Stille and Heck conditions across a set of common electrophiles and similar reaction parameters. The results are given in Table 3. Even though Stille protocols were competitive for some substrates, Heck conditions generally gave better yields in less reaction time.

Convinced that the Heck conditions were best, three (*E*)-vinyltributylgermanes fully substituted at the allylic carbon (**1a–c**) were reacted with various electrophiles using the conditions given in entry 8 of Table 2. Here, all reactions were stopped at 16 h so as to allow direct comparisons across entries. The results are given in Table 4.[19]

Product yields ranged from poor to moderate, but again the *Z*-products were favored. Electron-poor arenes tended to give higher yields, but lower *Z*/*E* selectivity. Activated arenes tended to give more of the *E*-product (entries 5–7) suggesting an admixture of mechanistic pathways. Ortho-substituted arenes (entries 8 and 9) were non-reactive, suggesting a strong steric influence. Interestingly, the lack of an oxygen at the allylic carbon of the vinyltributylgermane was problematic (entry 11) (vide infra). Lastly, (*Z*)-ICH=$CHCO_2Me$ and (*E*)-ICH=$CH(CH_2)_6CO_2Me$ did not couple (not shown).

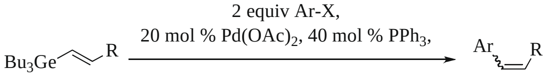
It was also noted that *Z*/*E* product ratios were concentration dependent. As Table 5 shows, increased reaction concentrations met with decreased *Z*/*E* ratios, but with relatively steady yields. For Heck-type reactions, elimination is proposed to be rate determining,[20] and should therefore be independent of concentration. However, the rate-determining transmetallation step of a Stille-

Table 3
Comparison of Heck and Stille conditions

Entry	Ar-X	% Yield (Stille A)[a]	% Yield (Stille B)[b]	% Yield (Heck)[c]
1	PhI	30	25	47
2	PhBr	28	28	26
3	1-Bromo-4-nitrobenzene	10	0	48

[a] Conditions A: 20 mol % Pd_2dba_3, 80 mol % $AsPh_3$, **1a**, 2 equiv ArX, NMP, 70 °C, 48 h.
[b] Conditions B: Same as conditions A using $Pd(OAc)_2$ instead of Pd_2dba_3.
[c] Heck conditions: 20 mol % $Pd(OAc)_2$, 40 mol % PPh_3, **1a**, 2 equiv ArX, 1 equiv K_2CO_3, 1 equiv Bu_4NBr, $MeCN/H_2O$ (9:1), 70 °C, 16 h.

Table 4
Reactions of vinyltributylgermanes (**1a–c**) with halides



1aŠc **2Š11**

Entry	Germane	Halide	% Yield (**2–11**)	*Z*/*E*[a]
1	**1a**	Bromobenzene	26 (**2**)	>20/1
2	**1a**	Iodobenzene	47 (**2**)	>20/1
3	**1a**	4-Iodotoluene	47 (**3**)	>20/1
4	**1a**	4-Bromoanisole	27 (**4**)	>20/1
5	**1a**	4-Bromoacetophenone	61 (**5**)	4.7/1
6	**1a**	Methyl 4-bromobenzoate	68 (**6**)	5/1
7	**1a**	1-Bromo-4-nitrobenzene	48 (**7**)	2.4/1
8	**1a**	2-Bromotoluene	0 (**8**)	—
9	**1a**	2-Bromoacetophenone	0 (**9**)	—
10	**1b**	4-Bromoacetophenone	61 (**10**)	>20/1
11	**1c**	4-Bromoacetophenone	0 (**11**)	—

[a] Yields and *Z*/*E* ratios based on isolated material.

Table 5
Concentration impact on *Z*/*E* ratios[a]

Entry	Molarity	% Yield **2**	*Z* % Yield	*E* % Yield	*Z*/*E*
1	0.1	29	27	2	13.5/1
2	0.168	26	21	5	4.2/1
3	0.2	23	17	6	2.8/1

[a] Reaction conditions from Table 4 entry 1, with the solvent adjusted to obtain the indicated molarity.

type reaction should be affected by vinyltributylgermane concentration. Thus the data suggest that the Stille pathway becomes kinetically competitive at higher molarities.

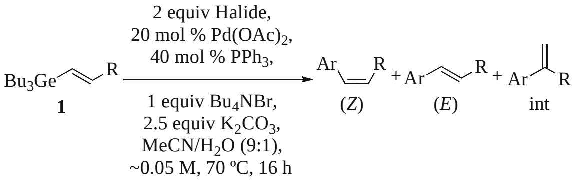
Next, we reacted vinyltributylgermanes that were not fully substituted at the allylic position. Within the context of our putative Heck mechanism, two carbons possessing β-hydrogens flank the Pd-intermediate formed upon addition across the olefin of such substrates. In theory this would allow us to probe any competition between Pd–Ge and Pd–H eliminations. The results are given in Table 6.

Interestingly, (*E*)-**1g** gave exclusively the cine (internal) product, albeit in only 15% yield. Regioisomeric mixtures of **1e**, **1d**, and **1i** each afforded mixtures of *E*-, *Z*-, and cine-products, with the cine products formed in yields exceeding the amounts of starting internal germane. Notably, submitting the starting material to the reaction conditions without the aryl bromide did not change the *E*/internal ratio. All these data suggest that (*E*)-vinyltributylgermanes unhindered at the allylic position give rise to cine substitution. This conclusion, in combination with low *Z*-product yields and no indication of Pd–H elimination, indicates the involvement of non-Heck pathways.

Lastly, we sought to test the stereospecificity of these reactions. To do so, we synthesized the *Z*-isomers of **1a** and **1j** by hydroboration of the corresponding germylalkynes followed by deborylation with acetic acid (Scheme 3).[21]

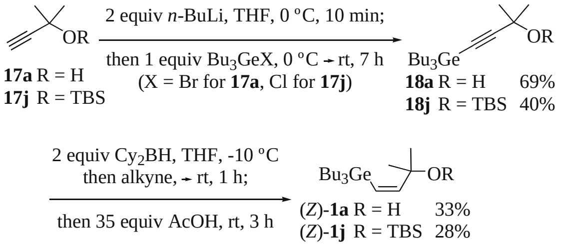
(*Z*)-Vinyltributylgermanes, so prepared, were reacted with Ph–I under our now standard conditions. Compound (*Z*)-**1a** coupled to a larger extent than (*E*)-**1a** (Table 7, entries 1 and 2) after 6 h, and with a much different level of stereoselectivity. (*E*)-**1a** required 16 h to achieve similar product yield. The dissimilar results between (*E*)- and (*Z*)-**1a** did not appear to be the consequence of starting material or product isomerization. Geometrically pure (*E*)-**2** was inert when resubjected to the reaction conditions. Similarly, subjecting (*Z*)-**1b** to the reaction conditions in the absence of an electrophile only led (after 10 h) to the destruction of the germane and small amounts of phenyl-coupled products (both *E* and *Z*), presumably from reaction with Ph_3P.[22] Slow addition of the germane gave the same results as when the germane was added in a single portion; providing further evidence against isomerization of the starting germane. The increased reactivity of the *Z*-germane is in keeping with Faller's finding that O-chelated germatranes are more reactive than C-chelated ones.[4a] We suggest that our system is undergoing a similar activation in which electron donation of the oxygen increases the reactivity of the germanium.[23] To this end, we synthesized the TBS ether (*Z*)-**1j** (Scheme 3) in order to shut down any chelation by the oxygen. When this substrate was subjected to our Heck conditions, only trace amounts of *Z*-product were observed by ^{1}H NMR analysis of the crude mixture after 6 and 24 h, supporting our hypothesis that oxygen activates the Stille pathway via germanium chelation.

Table 6
Reactions of unhindered vinyltributylgermanes



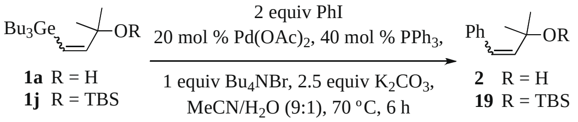
Entry	Germane	Halide	% Yield	*Z*/*E*/int
1	**1g**	4-Bromoacetophenone	15 (**12**)	100% int
3	**1e**[a]	4-Bromoacetophenone	49 (**13**)	4/1/20
4	**1d**[a]	Iodobenzene	35 (**14**)	5/1/19
5	**1d**[a]	4-Bromoacetophenone	49 (**15**)	3/1/20
6	**1i**[b]	4-Bromoacetophenone	39[c] (**16**)	2.1/1/7.1[c]
7	**1i**[d]	4-Bromoacetophenone	37[c] (**16**)	1.1/1/4.2[c]

[a] Starting *E*/internal ratio of 4/1.
[b] Starting *E*/internal ratio of 10/1.
[c] Determined by ^{1}H NMR analysis of the crude reaction using anisole as an internal standard.
[d] Starting *E*/internal ratio 4.3/1.



Scheme 3. Synthesis of (*Z*)-**1a** and (*Z*)-**1j**.

Table 7
Effect of vinyltributylgermane geometry[a]



Entry	Germane	% Yield	*Z* % Yield	*E* % Yield	*Z*/*E*
1	(*Z*)-**1a**	45 (**2**)	19	26	0.73/1
2	(*E*)-**1a**	35 (**2**)	31	4	8.8/1
3	(*Z*)-**1j**	Traces (**19**)	Traces	Not detected	*Z* only

[a] Yields and *Z*/*E* ratios determined by ^{1}H NMR analysis of the crude reaction using mesitylene as an internal standard.

In summary, vinyltributylgermanes react with aryl halides under Heck-type conditions. Depending on their degree of substitution, (*E*)-vinyltributylgermanes preferentially afford either the (*Z*)-alkenyl or cine products in moderate yields. Reaction concentration is among the factors that can affect the observed selectivities, suggesting an admixture of mechanistic pathways is operative. Efforts aimed at better defining those pathways and developing synthetically useful protocols that take full advantage of the intriguing and complementary nature of these reactions are ongoing.

Acknowledgment

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12. Faller and Kultyshev pointed out (Ref. 4a) the difficulty in assessing the extent to which, or even if, a Heck mechanism is operating during their chemistry. Under their conditions reaction of (*E*)-β-phenylethenylgermatrane with *p*-iodotoluene afforded the corresponding *E*-stilbene, whereas a 3.5/1 mixture of (*Z*/*E*)-β-phenylethenylgermatrane gave a 2.6/1 *Z*/*E*-mixture.
13. For reviews on the Heck reaction see: (a) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *33*, 2379–2411; (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
14. Et_3N, TlOEt, KOH, K_2PO_4, and CsF failed to afford **2**.
15. Anhydrous MeCN and dioxane failed to afford **2**.
16. These conditions are similar to the Heck conditions first described by Jefferey. See: (a) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051–3054; (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.
17. Biaryl formation tracks with electrophile activation. For example, PhBr gave 1–2% biaryl, while biaryl production with 1-bromo-4-nitrobenzene exceeded 20%.
18. Increasing the $Ph_3P/Pd(OAc)_2$ ratio inhibited the reaction.
19. Representative experimental: Bu_4NBr (0.1 mmol) and K_2CO_3 (0.3 mmol) were stirred in a mixture of $MeCN/H_2O$ (2 mL, 9:1) for 15 min. The vinyltributylgermane (0.1 mmol), PPh_3 (0.04 mmol), and halide (0.2 mmol) were added and the reaction mixture was stirred for 15 min. $Pd(OAc)_2$ (0.02 mmol) was added and the reaction mixture was aged at 70 °C for 16 h. The mixture was cooled to rt, quenched with satd NH_4Cl, and extracted with Et_2O. The organics were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by column chromatography on silica gel.
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23. Possible activation of the germanium by oxygen chelation: