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Stereocontrolled Formation of Styrenes by Pd(0)-catalyzed Cross-coupling of Photoactivated (*E*)-Alkenylgermanes with Aryl Bromides

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The stereocontrolled synthesis of (*E*)-configured styrenes via Pd(0)-catalyzed cross-couping of (*E*)-alkenylgermanes with aryl bromides is described. The germanes employed have bis(naphthalen-2-ylmethyl) substitution to allow photooxidative activation toward coupling and a C_8F_{17}-fluorous tag to facilitate purification by fluorous solid-phase extraction (F-SPE). The selectivities obtained suggest that a germyl-Stille rather than Heck-type mechanism predominates in the coupling step.

Biaryls and styrenes are key structural motifs in numerous bioactive natural products, pharmaceuticals, agrochemicals, dyes, organic semiconductors, and ligands/auxiliaries for asymmetric synthesis.[1] We recently described a new method for the preparation of biaryls via the Pd(0)-catalyzed germyl-Stille cross-coupling of light fluorous-tagged arylgermanes with aryl bromides following photochemical activation of the "safety-catch" arylgermane partner (Scheme 1).[2,3]

The method offers some unique features that make it potentially attractive for synthesis: the arylgermanes are easy to prepare, nontoxic[4] and inert to a wide range of reaction conditions, most notably those involving strong bases, nucleophiles, and reductants.[5] This allows the germyl unit to be installed early in a synthetic sequence, carried through subsequent elaboration steps with few restrictions on the types of reactions employed, although strongly acidic and oxidative conditions must be avoided, before selective activation by photooxidation to enable cross-coupling. The photooxidation itself is achieved by irradiation of a solution of the substrate and $Cu(BF_4)_2$ with a high-pressure Hg lamp for 2 h. This photolysis furnishes a difluorogermane reactive intermediate that can be used directly for cross-coupling after filtration and solvent-exchange.[6] The C_8F_{17} fluorous-tag on the germyl unit enables rapid purification of all intermediates by F-SPE prior to cross-coupling.[7]

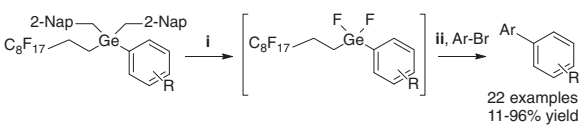
Here, we describe our preliminary exploration of the cross-coupling of light fluorous-tagged "safety-catch" terminal (*E*)-alkenylgermanes, which we anticipated to benefit from the same synthetic attributes as their aryl congeners, with aryl bromides following photochemical activation of the alkenylgermane partner. These reactions furnish the expected β-substituted styrenes, predominantly with retention of alkene (*E*)-stereochemistry, accompanied in some instances by lesser amounts of α-substituted isomers (i.e., products of *cine* rather than *ipso* cross-coupling). Mechanistic implications of these findings are discussed in relation to previously reported alkenylgermane[8] and analogous -silane[9] and -stannane[10] cross-coupling reactions.

Three light fluorous-tagged alkenylgermanes were employed in these studies: (*E*)-β-phenethylethenylgermane **3a**, (*E*)-β-phenylethenylgermane **3b**, and (*E*)-β-(methoxymethyl)-ethenylgermane **3c**. These derivatives were prepared with complete regio- and stereoselectivity by $[RhCl(CO)(PPh_3)_2]$-catalyzed hydrogermylation of the corresponding alkynes **2a**–**2c** with fluorous-tagged germyl hydride **1**[11] (Scheme 2).[12]

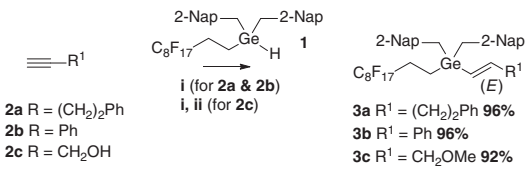
The high regio- and stereoselectivities are probably attributable to the bulky bis(naphthalen-2-ylmethyl) groups on the germanium hydride **1**. Assignment of the product stereochemistries as (*E*) followed from ^{1}H NMR analysis of their vicinal alkenyl coupling constants ($^3J \approx 18$ Hz).

Photolytic activation of (*E*)-alkenylgermanes **3a**–**3c** under the conditions developed previously by us for arylgermanes[3] resulted in smooth conversion to the corresponding (*E*)-alkenyldifluorogermanes **4a**–**4c**. An alkenyl ^3J value of ≈18 Hz in the ^{1}H NMR spectrum of derivative **4a** confirmed that no photoisomerization had occurred. Without purification, these difluorogermanes were immediately subject to Pd(0)-catalyzed cross-coupling with a selection of aryl bromides again under the conditions previously developed for biaryl coupling (Table 1).[3]

In all cases, moderate to good yields of isolated styrenyl products **5** were obtained, and a single major β-substituted isomer predominated although the coupling of germane **3a** with relatively electron-rich aryl bromides resulted in the formation of significant amounts of the α-substituted isomers (i.e., products of *cine* cross-coupling, Entries 6–8). Assignment of the stereochemistry of the major (*E*)- and minor (*Z*)-β-substituted styrenes was straightforward on the basis of

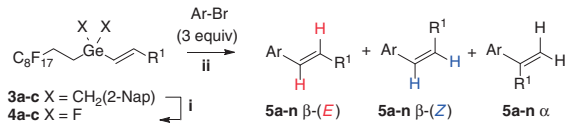


Scheme 1. Activation and Pd(0)-mediated cross-coupling of light fluorous-taged "safety-catch" arylgermanes (refs. 2 and 3). *Conditions*: i) *hν*, Pyrex tube, $Cu(BF_4)_2$ (2 × 4 equiv), MeOH/MeCN (3:1), 2 h; ii) $[PdCl_2(MeCN)_2]$ (10 mol %), (*o*-Tol)$_3$P (15 mol %), TBAF·3H$_2$O (2.7 equiv), CuI (1 equiv), DMF, 120 °C, 16 h.



Scheme 2. Synthesis of light fluorous-tagged (*E*)-β-ethenylgermanes **3a**–**3c** by Ru(I)-catalyzed hydrogermylation. *Conditions*: i) $[RhCl(CO)(PPh_3)_2]$ (5 mol %), CH_2Cl_2, 40 °C, 24 h (→**3a** and **3b**) or $Cl(CH_2)_2Cl$, 80 °C, 16 h (→**3c**); ii) NaH (2 equiv), Me_2SO_4 (2.3 equiv), THF, 0–23 °C, 2 h.

Table 1. Substrate scope of Pd(0)-catalyzed cross-coupling of (*E*)-alkenylgermanes **3a**–**3c** with alkenyl bromides[a]



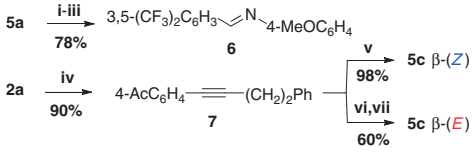
Entry	R^1	Ar	Product	Yield /%	Isomer ratio[b] β-(*E*):β-(*Z*):α
1	$(CH_2)_2Ph$	3,5-$(CF_3)_2C_6H_3$	**5a**	65	98:2:0
2	$(CH_2)_2Ph$	4-CNC_6H_4	**5b**	65	99:1:0
3	$(CH_2)_2Ph$	4-AcC_6H_4	**5c**	59	100:0:0
4	$(CH_2)_2Ph$	3,5-$(CH_3)_2C_6H_3$	**5d**	63	93:5:2
5	$(CH_2)_2Ph$	4-FC_6H_4	**5e**	58	93:2:5
6	$(CH_2)_2Ph$	4-ClC_6H_4	**5f**	52	73:1:26
7	$(CH_2)_2Ph$	4-MeC_6H_4	**5g**	72	80:8:12
8	$(CH_2)_2Ph$	4-$MeOC_6H_4$	**5h**	40	67:13:20
9	$(CH_2)_2Ph$	2-$NO_2C_6H_4$	**5i**	48	80:20:0
10	Ph	3,5-$(CF_3)_2C_6H_3$	**5j**	58	82:17:1
11	Ph	4-CNC_6H_4	**5k**	60	90:10:0
12	Ph	4-AcC_6H_4	**5l**	66	100:0:0
13	Ph	4-MeC_6H_4	**5m**	52	99:1:0
14	CH_2OMe	4-AcC_6H_4	**5n**	72	99:1:0

[a]*Conditions*: i) *hν*, Pyrex tube, $Cu(BF_4)_2$ (2 × 4 equiv), MeOH/MeCN (3:1), 2 h; ii) $[PdCl_2(MeCN)_2]$ (10 mol %), $(o\text{-Tol})_3P$ (15 mol %), $TBAF\cdot 3H_2O$ (2.7 equiv), CuI (1 equiv), DMF, 120 °C, 16 h. [b]Isomeric ratios determined by GC-MS and ^{1}H NMR analysis.

^{1}H NMR alkene ^3J values [i.e., (*E*) ^3J = 15–18 Hz vs. (*Z*) ^3J = ≈10–12 Hz] for products **5d**–**5n** (Entries 4–14). By contrast, the major β-substituted styrenyl products **5a**–**5c** obtained from coupling germane **3a** with 3,5-$(CF_3)_2C_6H_3$Br, 4-CNC_6H_4Br, and 4-AcC_6H_4Br (Entries 1–3) displayed very similar but complex second-order distortion patterns in the alkene region of their ^{1}H NMR spectra due to the two protons being close in chemical shift; this gave these spectra a very distinctive appearance and prevented assignment by alkene ^3J value analysis.[13] Ozonolysis of styrene **5a** followed by reductive cleavage and in situ reaction with 4-anisidine afforded imine **6** (78% overall yield) which confirmed these major coupling adducts to be β-styrenes. Unambiguous stereochemical assignment followed from independent synthesis of both isomers of β-styrene **5c**. (*Z*)-β-Styrene **5c** was prepared by the Sonogashira cross-coupling of alkyne **2a** with 4-AcC_6H_4I to give arylalkyne **7** then Lindlar partial hydrogenation. (*E*)-β-Styrene **5c** was obtained via Ru(I)-catalyzed hydrosilylation of alkyne **7** followed by TBAF-mediated protodesilylation[14] (Scheme 3).

Comparison of the ^{1}H NMR spectra of these authentic samples with the cross-coupling adduct obtained from (*E*)-alkenylgermane **3a** (Entry 1, Table 1) confirmed that (*E*)-β-styrene **5c** was the major isomer, as in all the other cases (Figure 1).

We hypothesized that improved stereoselectivity for the desired β-(*E*)- over β-(*Z*)- and/or α-styrene isomers in these photoactivated reactions might be achieved by tuning the phosphine present during the Pd(0)-catalyzed cross-coupling step. The coupling between germane **3a** and 4-MeC_6H_4Br,



Scheme 3. Experiments to confirm the regio- and stereochemical assignments of styrenyl cross-coupling products **5a** and **5c**. *Conditions*: i) O_3, CH_2Cl_2, −78 °C, 10 min; ii) PPh_3 (2.5 equiv), CH_2Cl_2, 0–23 °C, 1 h; iii) 4-anisidine (1.5 equiv), CH_2Cl_2, 2 h; iv) 4-AcC_6H_4I (1.0 equiv), $[PdCl_2(PPh_3)_2]$ (3 mol %), TBAF (2 equiv), CuI (3 mol %), THF, 16 h; v) H_2 (1 atm), Lindlar's catalyst (Pd/Pb), EtOAc, 2 h; vi) $[Cp^*Ru(MeCN)_3]^+PF_6^-$ (1 mol %), $(EtO)_3SiH$ (1.2 equiv), CH_2Cl_2, 16 h; vii) CuI (1.5 equiv), TBAF (3 equiv), THF, 16 h.

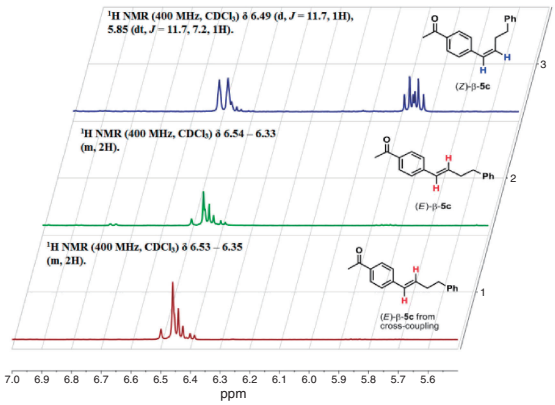
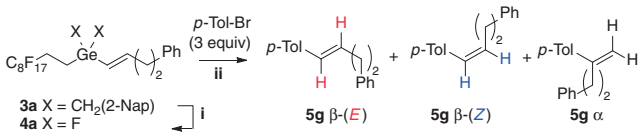


Figure 1. Comparison of ^{1}H NMR spectra of alkene region of: a) authentic (*Z*)-β-**5c**, b) authentic (*E*)-β-**5c**, and c) (*E*)-β-**5c** from cross-coupling of alkenylgermane **3a** with 4-AcC_6H_4Br (Entry 3, Table 1).

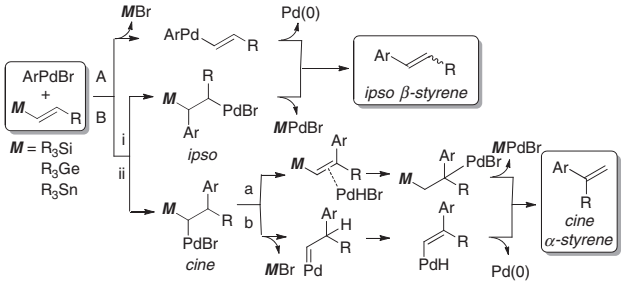
Table 2. Screening of phosphine ligands to effect more (*E*)-stereoselective β-styrene formation[a]



Entry	Phosphine	Yield /%	Isomer ratio β-(*E*):β-(*Z*):α
1	*t*-BuXPhos	65	94:5:1
2	$(n\text{-Bu})_3P$	62	98:1:1
3	$Cy_3P\cdot HBF_4$[b]	71	100:0:0
4	dppp	42	100:0:0

[a]*Conditions*: i) *hν*, Pyrex tube, $Cu(BF_4)_2$ (2 × 4 equiv), MeOH/MeCN (3:1), 2 h; ii) $[PdCl_2(MeCN)_2]$ (10 mol %), phosphine (15 mol %), $TBAF\cdot 3H_2O$ (2.7 equiv), CuI (1 equiv), DMF, 120 °C, 16 h. [b]Addition of $i\text{-Pr}_2NEt$ (15 mol %).

which gave a 80:8:12 ratio of β-(*E*):β-(*Z*):α isomeric products with $(o\text{-Tol})_3P$ (Entry 7, Table 1), was selected as a test reaction on which to screen four alternative phosphines: *t*-BuXPhos, $(n\text{-Bu})_3P$, Cy_3P, and dppp (Table 2).



Scheme 4. Proposed reaction pathways for alkenyl group 14 metal cross-coupling reactions.

All four phosphines furnished (*E*)-β-styrene **5g** with improved selectivity relative to the original (*o*-Tol)$_3$P-catalyzed conditions (Entry 7, Table 1). Sterically hindered electron-rich ligand *t*-BuXPhos and (*n*-Bu)$_3$P both gave high levels of (*E*)-selectivity (Entries 1 and 2, Table 2), but superior (*E*)-selectivity still was obtained by employing $Cy_3P{\cdot}HBF_4$ and dppp, with the former also delivering the highest yield (71%), making it the phosphine of choice for this reaction (Entries 3 and 4, Table 2).

In general, Pd(0)-catalyzed cross-coupling of (*E*)-alkenylsilanes and -stannanes with aryl (pseudo)halides are highly selective and furnish *ipso*-products with retention of the regio- and stereochemistry of the alkenylmetals employed.[15] This is attributed to a Stille-type pathway involving rapid transmetalation with the ArPd(II) complex followed by reductive elimination (route A, Scheme 4).

However, stereochemical leakage and/or formation of *cine*-products (i.e., α-substituted styrenes) can also occur for alkenylsilanes[9] and -stannanes[10] as the result of Heck-type pathways initiated by carbopalladation (route B). Steric and electronic factors determine the ratio of *ipso* vs. *cine* addition (i.e., route i vs. ii) with α-styrenyl products being formed from the *cine* carbopalladation intermediate via either a Kikukawa-type Pd–H elimination/readdition pathway (route a)[9a,9f,9h] or a Busacca-type Pd–carbene pathway (route b).[10a,10d,10e,16] Analogous pathways have been invoked for alkenylgermane cross-coupling reactions. These often display particularly poor regio- and stereocontrol.[8] Indeed, uniquely, (*E*)-alkenyltributylgermanes react under certain conditions to give predominantly (*Z*)-*ipso* and *cine* products.[8h] By comparison, our method gives high levels of selectivity for (*E*)-*ipso* products, presumably via a germyl-Stille pathway (cf. route A), although further experiments will be necessary to substantiate this.

In conclusion, a stereocontrolled method for the synthesis of (*E*)-configured styrenes via Pd(0)-catalyzed cross-couping of (*E*)-alkenylgermanes with aryl bromides has been developed. The alkenylgermanes are activated by photooxidation and a C_8F_{17}-fluorous tag facilitates purification by fluorous SPE prior to coupling. Unlike several previous alkenylgermane cross-coupling reactions, a germyl-Stille rather than Heck-type mechanism appears to predominate, possibly reflecting the unique intermediacy of difluorogermanes (cf. **4a**–**4c**) in these reactions. Application of this method for the parallel synthesis of bioactive styrene derivatives is currently under investigation.

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