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Pd-catalyzed couplings of (α-fluoro)vinyl tris(trimethylsilyl)germanes

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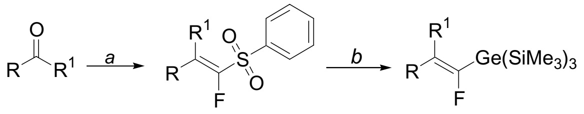
Abstract—The (α-fluoro)vinyl tris(trimethylsilyl)germanes undergo Pd-catalyzed cross-couplings with aryl and alkenyl halides upon oxidative treatment with hydrogen peroxide under basic aqueous conditions to give access to fluoroalkenes and fluorodienes with retention of stereochemistry.

Despite the wide application of organostannanes and organosilanes to coupling reactions,[1] only a few reports deal with application of organogermanes to Pd-catalyzed couplings,[2,3] although germanium is located between silicon and tin in the periodic table. Development of organogermanes as transmetalation reagents in Pd-catalyzed cross-coupling reactions has been limited by the complexity in their synthesis and lower reactivity of tetracoordinated organogermanium species (e.g., carbon–germane bonds are thermally more stable and chemically less reactive than carbon–tin bonds).[4] Aryl and alkenyl carbagermatrane[2a] and oxagermatrane[2b,d] derivatives developed by Kosugi and Faller and their co-workers were found to be more reactive than tetracoordinated germanes in cross-coupling reactions with aryl halides owing to the internal coordination of nitrogen to germanium. Couplings with organogermatranes were found to be promoted by fluoride (as in a case of organosilanes[1]) and addition of extra ligands.[2a–d] Oshima and co-workers showed that aryltri(2-furyl)germanes are viable reagents for biaryl synthesis,[2c] and Kosugi and co-workers demonstrated that easily accessible arylgermanium trichlorides undergo coupling with aryl halides in aqueous medium with NaOH in the presence of $Pd(OAc)_2$.[2e] We recently reported that vinyl tris(trimethylsilyl)germanes (TTMS-germane) can be employed in Pd-catalyzed coupling reactions with aryl and alkenyl halides.[3]

Application of (α-fluoro)vinyl stannanes and silanes as transmetalation reagents in Pd-catalyzed couplings has been limited as well. For example, the (α-fluoro)vinylstannanes provided only a moderate yield of coupling products with aryl iodides[5a] although in combination with CuI they are much better substrates for Stille coupling.[5] Also only one example of CsF-assisted coupling involving (α-fluoro)vinyl silanes [e.g., (1-fluorovinyl)methyldiphenylsilane] has been reported.[6] Herein, we report application of (α-fluoro)vinyl tris(trimethylsilyl)germanes as transmetalation reagents in Pd-catalyzed cross-coupling reactions with aryl halides and alkenyl bromides under oxidative conditions to give stereoselectively access to fluoroalkenes and fluorodienes.

The (α-fluoro)vinyl TTMS-germane precursors **3a–c**, a class of fluoroalkenes which remain unexplored, were prepared (50–80%) by stereoselective radical-mediated germyldesulfonylations[3a] (Scheme 1) of the (α-fluoro)vinyl sulfones **2a–c** with $(Me_3Si)_3GeH$[7] (Table 1).[8] The sulfones **2a–c**, in turn, were prepared by Wittig–Horner treatment of the corresponding conjugated **1a**



1 **2** **3**

Scheme 1. Reagents and conditions: (a) $PhSO_2CHFPO(OEt)_2$/LHMDS/THF/−78 °C; (b) $(Me_3Si)_3GeH$/AIBN/benzene/80 °C.

Keywords: Organogermanes; Cross-coupling reactions; Fluoroalkenes; Fluorodienes.

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Table 1. Synthesis of (α-fluoro)vinyl tris(trimethylsilyl)germanes **3**

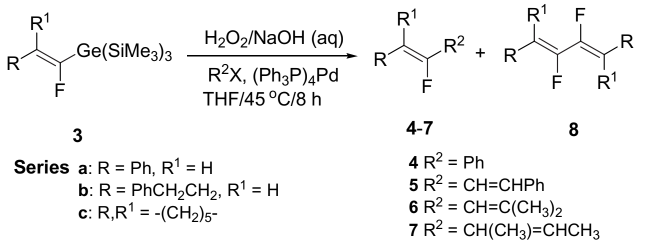
Entry	Substrate (E/Z)[b]	R	R^1	Product (E/Z)[b]	Yield[a] (%)
1	**2a** (94/6)	Ph	H	**3a** (98/2)	80
2	**2b** (70/30)	$PhCH_2CH_2$	H	**3b** (93/7)	50
3	**2c**	$–(CH_2)_5–$		**3c**	67

[a] Isolated yields, *E*-isomer only.

[b] Ratio of isomers based on ^1H and/or ^{19}F NMR of the crude reaction mixtures.

and nonconjugated **1b** aldehydes as well as cyclic ketone **1c** with diethyl fluoro(phenylsulfonyl)methylphosphonate[3a] according to the McCarthy procedure.[9] It is noteworthy that 1-fluoroalkynes are unstable and virtually unknown,[10] therefore, the synthesis of (α-fluoro)vinyl germanes via hydrogermylation[4,11] approaches are inapplicable.

Treatment of the (α-fluoro)vinyl germane **3a**(*E*) with H_2O_2 in the presence of NaOH in aqueous THF followed by the addition of iodobenzene and $Pd(PPh_3)_4$ (Scheme 2), gave fluoro stilbene **4a**(*Z*) stereoselectively (88%, Table 2, entry 1).[12] The nonconjugated **3b**(*E*) and β,β′-disubstituted **3c** (α-fluoro)vinyl germanes also underwent coupling with iodobenzene to give **4b**(*Z*) (75%, entry 7) and **4c** (85%, entry 9). Analogous coupling of **3a–c** with bromobenzene afforded the expected fluoro alkenes **4a–c** in lower yields (24–30%, entries 2, 8, and 10). The major by-products isolated from the reaction mixtures were the corresponding 1,4-disubstituted (*Z*,*Z*)-2,3-difluoro-1,3-butadienes **8a**[5b] (35%, i.e., 70% consumption of **3a**; entry 2) or **8b** (60%, entry 8) or 1,1′,4,4′-tetrasubstituted butadiene **8c** (26%, entry 10). Not surprisingly, the chlorobenzene was less effective as electrophile[13] [e.g., attempted coupling with **3a** gave dimer **8a** predominantly (80%, entry 3)]. Thus, the (α-fluoro)vinyl TTMS-germanes **3a–c** undergo coupling with aryl iodide with no difficulty, while couplings with aryl bromides compete with oxidative self-coupling of germanes **3**, and the reactions with aryl chlorides lead to the almost exclusive formation of self-coupled dimers **8**.



Scheme 2.

The vinyl halides can be also employed in cross-coupling with organogermanes. Thus, oxidative treatment of **3a**(*E*) (H_2O_2/NaOH) followed by addition of $Pd(PPh_3)_4$ and β-bromostyrene (*E*/*Z*, ~88:12; 1.5 equiv) gave (1*Z*, 3*E*)-2-fluoro-1,4-diphenyl-1,3-butadiene (**5a**; 92%, entry 4). The aliphatic vinyl bromide, 1-bromo-2-methyl-1-propene, also coupled with organogermanes **3a** and **3c** to give products **6a** and **6c** in 72% and 65% yields in addition to homocoupled byproducts **8a** and **8c** (entries 5 and 11). Even the secondary vinyl bromide, 2-bromo-2-butene (3.0 equiv, *E*/*Z*, ~1:1), underwent coupling with organogermane **3a**(*E*) to give **7a**(*Z*,*E*) although in lower yield (26%, entry 6). The coupling was *trans* selective with regards to the vinyl bromides since no traces of the geometric isomers [e.g., **7a**(*Z*,*Z*), GC–MS] were detected in the reaction mixture. These are interesting results since the unfluorinated vinyl TTMS-germanes failed to couple with the aliphatic vinyl bromides.[3b] The results are encouraging because the presence of fluorine in the substrates for Stille[5] and Hiyama[6,14] couplings impede their reactivity as nucleophilic transmetalation components. Faller et al. reported that arylalkynyl oxagermatranes underwent couplings with less reactive aryl chlorides and triflates under milder conditions that are usually required for Sonogashira coupling reactions with triorganosilicon reagents.[2d]

Table 2. Pd-catalyzed coupling of (α-fluoro)vinyl tris(trimethylsilyl)germanes **3**

Entry	Substrate	R^2X	Product	Yield[a] (%)	Dimer **8**[a,b] (%)
1	**3a**(*E*)[c]	PhI	**4a**(*Z*)	88	n.d.[d]
2	**3a**(*E*)	PhBr	**4a**(*Z*)	24	**8a** (70)
3	**3a**(*E*)	PhCl	**4a**(*Z*)	5	**8a** (80)
4	**3a**(*E*)	PhCH=CHBr[e]	**5a**(*Z*,*E*)	92	n.d.[d]
5	**3a**(*E*)	$(CH_3)_2C$=CHBr	**6a**(*Z*)	72	**8a** (20)
6	**3a**(*E*)	CH_3CH=C(CH_3)Br[f]	**7a**(*Z*,*E*)	26	**8a** (71)
7	**3b**(*E*)	PhI	**4b**(*Z*)	75	n.d.[d]
8	**3b**(*E*)	PhBr	**4b**(*Z*)	30	**8b** (60)
9	**3c**	PhI	**4c**	85	n.d.[d]
10	**3c**	PhBr	**4c**	30	**8c** (26)
11	**3c**	$(CH_3)_2C$=CHBr	**6c**	65	**8c** (30)

[a] Isolated yields.

[b] Yields are based on the consumption of substrates **3**. Only *Z*,*Z* dimers of **8a** and **8b** were observed (GC–MS).

[c] Coupling in the presence of $Pd_2(dba)_3$ gave **4a**(*Z*) (70%) and **8a** (20%).

[d] Not detected (GC–MS).

[e] *E*/*Z* = 88:12.

[f] *E*/*Z* = 1:1, (3 equiv).

The only by-products isolated from the cross-coupling reactions were 2,3-difluoro-1,3-dienes **8** resulting from the oxidative homocoupling of (α-fluoro)vinyl TTMS-germanes.[15] Surprisingly, reductive homocoupling of halide components has not been observed, although they were often formed during attempted cross-couplings with organogermanes (12–60%),[2b] including vinyl TTMS-germanes (5–20%).[3b] It is also noteworthy that no addition of extra ligands[2e] such as $PhAr_3$,[2a] $AsPh_3$,[2b] $(2\text{-furyl})_3P$,[2b,c] or Bu^t_2P(biphenyl)[2b,2d] was required for the coupling reaction to occur with TTMS-germanes when $Pd(Ph_3)_4$ was used as Pd source. Moreover, coupling of **3a** with iodobenzene in the presence of $Pd_2(dba)_3$ afforded **4a**(*Z*) in 70% yield in addition to dimer **8a** (20%). Attempted couplings of germanes **3a–c** with iodobenzene and bromobenzene under oxidative anhydrous conditions (*tert*-butylperoxide/KH/THF)[3b,16] failed to give the corresponding coupled products **4**–**7**.

It appears that hydrogen peroxide cleaves the Ge–Si bond(s) in **3a–c** $[R'Ge(SiMe_3)_3]$ to generate active germanol or germanoxane species[17] of the type $R'Ge(OH)_n(SiMe_3)_{3-n}$ or $R'Ge(OSiMe_3)_n(SiMe_3)_{3-n}$ ($n = 1, 2, \text{or } 3$). Cleavage of Ge–Si bond under oxidative conditions via oxygen insertion has been reported.[18] To obtain mechanistic insights of this process, we examined the coupling reaction of **3a**(*E*) with iodobenzene in THF-d_8 directly in an NMR tube. After adding H_2O_2, the ^{19}F peak of substrate **3a**(*E*) [δ: -81.93 (d, $J = 51.4$ Hz)] quickly disappeared (~5 min, ambient temperature) and a new signal appeared as doublet ($J = 50.8$ Hz) of multiplets at δ -101.42. With the subsequent addition of iodobenzene and Pd(0) catalyst the peak for the fluoro stilbene **4a**(*Z*) gradually was formed at δ -114.64 ppm (d, $J = 39.5$ Hz). Furthermore, the TTMS peak of substrate **3a**(*E*) [δ: 0.34 (s)] was shifted upfield (Δ 0.33 ppm) on the ^1H NMR spectra upon addition of H_2O_2. These observations indicate that TTMS-germane **3a**(*E*) reacts with H_2O_2 generating a new intermediate, possibly a germanol or a germanoxane, which subsequently undergoes coupling.

In summary, we have demonstrated that conjugated and nonconjugated (α-fluoro)vinyl tris(trimethylsilyl)-germanes successfully undergo Pd-catalyzed cross-couplings with aryl and alkenyl halides under aqueous oxidative conditions to produce fluoroalkenes and fluorodienes with retention of stereochemistry. Couplings with the (α-fluoro)vinyl TTMS-germanes appeared to more facile than with the corresponding (α-fluoro)vinyl stannanes and silanes since neither addition of an extra ligand nor activation with CuI or fluoride was required.

Acknowledgements

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12. (a) (*Z*)-1-Fluoro-1,2-diphenylethene (**4a**): Coupling procedure—A solution of NaOH (12 mg, 0.3 mmol) and H_2O_2 (30% solution, 20 μL, 0.20 mmol) in deionized H_2O (0.35 mL) was added to a stirred solution of **3a**[3a] (26 mg, 0.063 mmol) in THF (3 mL) at ambient temperature. After 15 min, iodobenzene (11 μL, 20 mg, 0.095 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) were added and the resulting brownish mixture was heated at 45 °C (oil bath) for 8 h. The volatiles were evaporated, and the residue was partitioned ($H_2O/CHCl_3$). The organic layer was dried ($MgSO_4$), evaporated, and purified by column chromatography (hexane) to give **4a** (11 mg, 88%) with data as reported:[5b] ^{19}F NMR δ −114.64 (d, $J = 39.5$ Hz). (b) **5a**: ^{1}H NMR δ 5.82 (d, $J = 38.2$ Hz, 1H), 6.65 (dd, $J = 25.2$, 15.9 Hz, 1H), 7.00 (d, $J = 15.9$ Hz, 1H), 7.25–7.32 (m, 2H), 7.38 (t, $J = 7.7$ Hz, 4H), 7.46–7.52 (m, 2H), 7.61 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR δ 111.05 (d, $J = 9.9$ Hz, C1), 121.20 (d, $J = 22.7$ Hz, C3), 127.22 (Ph), 127.78 (d, $J = 2.0$ Hz, Ph), 128.68 (Ph), 128.98 (Ph), 129.18 (Ph), 129.24 (Ph), 129.32 (Ph), 130.06 (d, $J = 4.2$ Hz, C4), 134.28 (d, $J = 3.3$ Hz, Ph), 136.58 (Ph), 157.53 (d, $J = 259.7$ Hz, C2); ^{19}F NMR δ −118.17 (dd, $J = 38.2$, 25.2 Hz); GC–MS (t_R 19.94 min) *m*/*z* 224 (100, M^+). FAB-HRMS Calcd for $C_{16}H_{13}F$ (MH^+): 225.1080. Found: 225.1090. (c) **6c**: ^{1}H NMR δ 1.57 (br s, 6H), 2.07 (br s, 2H), 2.17 (s, 3H), 2.27 (s, 3H), 2.34 (br s, 2H), 5.68 (d, $J = 19.0$ Hz, 1H); ^{19}F NMR δ −117.22 (d, $J = 19.5$ Hz); GC–MS (t_R 8.34 min) *m*/*z* 168 (100, M^+). FAB-HRMS Calcd for $C_{11}H_{17}F$ (MH^+): 169.1393. Found: 169.1401.
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