Highly Regio- and Stereoselective Hydrogermylation of Fluorinated Alkyl Propiolate

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Abstract The selective introduction of fluoroalkylated vinylmetals in controlled strategies is a challenging process for many chemists. This study reports the highly regio- and stereoselective synthesis of functionalized vinylgermanes bearing a perfluoroalkyl group from perfluoroalkylated acetylenic esters via AlCl₃-catalyzed hydrogermylation. Regio- and stereoselectivity are highly dependent on the nature of the catalyst and the nature of the fluoroalkyl group of alkyne.

Key words regio- and stereoselective hydrogermylation, fluorinated ethyl propiolate, AlCl₃, triphenyl- and tributylgermanes, fluorinated vinylgermanes

The selective introduction of fluoroalkylated vinylmetals in controlled strategies is a challenging process for many chemists. This study reports the highly regio- and stereoselective synthesis of functionalized vinylgermanes bearing a perfluoroalkyl group from perfluoroalkylated acetylenic esters via AlCl₃-catalyzed hydrogermylation. Regio- and stereoselectivity are highly dependent on the nature of the catalyst and the nature of the fluoroalkyl group of alkyne.

There are a few synthetic strategies that enable such an operation including the direct sp² C–H bond functionalization,⁷ and olefination reactions.⁸ However, these methods suffer from limitations and stereoselectivity issues. Provided that regio- and stereoselectivity of the hydrometallation could be controlled, an efficient approach that would afford a straightforward entry to the selective preparation of low toxic fluoro-polysubstituted alkenes would rely on the hydrogermylation/cross coupling sequences from alkynes bearing fluorinated moieties. Although, germanium is slightly more expensive than tin, it is closer to silicon in its organic chemistry. Furthermore, germanium has a higher thermal stability,⁹ and a lower toxicity than tin.¹⁰

The addition of organogermandes to alkynes is the best method for the direct synthesis of vinylgermanes.¹¹,¹² However, hydrogermylation of carbonyl functionalized fluorinated alkenes, which provides a new entry to a wide range of functional fluorinated compounds, is still under investigation. To our knowledge, no hydrogermylation reaction of fluorinated alkenes type ¹ ¹ a¹³ has been described in the open literature. It is worth mentioning that we recently reported the first highly regio- and stereoselective free-metal hydrostannylation of ethyl 4,4,4-trifluorobut-2-ynoate (¹ ¹ a) leading to the synthesis of α and β-tributylstannyl-4,4,4-trifluorobut-2-enoates without any additives (Scheme 1).¹⁴

![Scheme 1](https://example.com/scheme.png)
As a continuation of our previous study on the hydrogermylation reaction of fluorinated alkynes for the preparation of new vinylmetal compounds using a perfluoroalkyl group, we report herein, for the first time, a highly regio- and stereoselective hydrogermylation reaction of fluorinated alkynes of type 1 using the inexpensive Lewis acid AlCl₃ as catalyst.

We first sought to determine the best conditions for a highly regio- and stereoselective hydrogermylation reaction of fluorinated alkyl propiolate 1a with Ph₃GeH using different solvents and additives. The results are summarized in Table 1.

First, we examined the free-metal hydrogermylation of 1a using triphenylerganium hydride in different solvents. Importantly, and contrary to what is generally observed in the case of hydrosilylation of alkynes 1a, the regioselectivity of this hydrogermylation reaction is relatively independent of the nature of the solvent (Table 1, entries 1–3). Thus, using hexane, methanol or dichloromethane as solvent, the hydrogermylation of alkyl 1a leads to the formation of the four possible isomers (Z)-2a, (E)-2a, (Z)-2b and (E)-2b. In all cases, the regioselectivity is greatly in favor of the β-regioisomer (>75%). Although the ratio of formation of both α- and β-adducts is not exactly the same in each selected solvent, it is clear that the polarity of the solvents does not have a significant impact on the hydrogermylation reaction.

The regiochemistry of vinylgermanes was then deduced without ambiguity from NMR data, especially from the 1H and 19F NMR spectra of the crude hydrogermylation product (Table 1, entry 6). A majority of the hydrogermylation reaction proceeds mainly by a free radical mechanism. Organogermanium hydrides have been used for the radical and transition-metal-catalyzed hydrogermylation of alkynes since the mid-1950s, but such transformations still suffer from serious limitations such as low regio- and stereoselectivities. However, Blanchard et al. developed two efficient stereo-complementary routes for nonfunctionalized (Z)- and (E)-α-trifluoromethylvinylgermanes by regio- and stereoselective hydrogermylation of α-trifluoromethylated alkynes under transition-metal-catalyzed conditions or in presence of a radical initiator.

Inspired by these results, fluorinated alkyl 1a was treated in dichloromethane with 1 equivalent of Ph₃GeH in the presence of a catalytic amount of Pd(PPh₃)₄ (5 mol%). The 1H and 19F NMR spectra of the crude hydrogermylation product reveal a 60:40 mixture of the α and β regioisomers was formed, respectively (entry 5). The (E)-2u adduct, resulting from a cis-addition, constitutes the major product.

To explore more synthetic routes to perform the highly regio- and stereoselective hydrogermylation of alkyn 1a, we next directed our attention to the hydrogermylation of alkyl 1a. The treatment of alkyl 1a with Ph₃GeH at room temperature using ammonium persulfate as radical initiator in aqueous acetonitrile, provides a mixture of the α- and β-regioisomers in a ratio of about 22:78, with a majority of the trans-addition product (Z)-2b (Table 1, entry 6). Similar results were obtained but with a lower yield when we used the known radical initiator triethylborane BEt₃ (entries 7).

Another class of catalyzed hydrogermylation reaction of functionalized alkynes was reported in 2005 based on the use of an expensive Lewis acid such as B(C₆F₅)₃. Gevorgyan et al. demonstrated that the stereochemistry of this hydrogermylation reaction depends on the nature of the alkylene used; the reaction proceeded via a trans-addition pathway with simple alkynes and cis-addition with ethyl propiolate. Applying the same conditions as Gevorgyan et al., by using BPh₃, a less expensive Lewis acid than B(C₆F₅)₃, the hydrogermylation of alkyl 1a with Ph₃GeH proceeds mainly by trans-addition, yielding the major product (Z)-2b with a small amount of the α-adduct (entry 8).

Lewis acid AlCl₃ mediated hydrosilylation and hydrostannylation of alkynes have been reported, but AlCl₃ has never been used in the case of the hydrogermylation of alkynes. We therefore decided to perform the hydrogermylation reaction of alkyl 1a at room temperature in the presence of a catalytic amount of AlCl₃ (10 mol%) in toluene during 2 h. Remarkably, complete α-regioselectivity of the hydrogermylation of alkyn 1a was observed, yielding α-triphenylgermylacrylate 2a as the sole regioisomer in 74% yield (Table 1, entry 9). Furthermore, the stereoselectivity was also greatly in favor of the (E)-isomer (E > 93%). Surprisingly, complete regio- and stereoselectivity of the hydrogermylation reaction was observed in the presence of...
Table 1 Hydrogermylation Reaction Conditions for 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive (%)</th>
<th>α/β</th>
<th>(Z)-2a (%)</th>
<th>(E)-2a (%)</th>
<th>(Z)-2β (%)</th>
<th>(E)-2β (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>methanol</td>
<td>–</td>
<td>24:76</td>
<td>14.0</td>
<td>9.8</td>
<td>68.9</td>
<td>6.3</td>
<td>39(^a)</td>
</tr>
<tr>
<td>2</td>
<td>hexane</td>
<td>–</td>
<td>24:76</td>
<td>13.2</td>
<td>10.4</td>
<td>68.3</td>
<td>7.8</td>
<td>35(^a)</td>
</tr>
<tr>
<td>3</td>
<td>CH(_2)Cl(_2)</td>
<td>–</td>
<td>20:80</td>
<td>14.8</td>
<td>5.5</td>
<td>78.1</td>
<td>1.6</td>
<td>65(^a)</td>
</tr>
<tr>
<td>4</td>
<td>CH(_2)Cl(_2)</td>
<td>TEMPO</td>
<td>100:0</td>
<td>36.0</td>
<td>64.0</td>
<td>0.0</td>
<td>0.0</td>
<td>21(^b)</td>
</tr>
<tr>
<td>5</td>
<td>CH(_2)Cl(_2)</td>
<td>Pd(PPh(_3))(5)</td>
<td>60:40</td>
<td>0.7</td>
<td>59.5</td>
<td>29.7</td>
<td>10.1</td>
<td>31(^a)</td>
</tr>
<tr>
<td>6</td>
<td>CH(_2)CN/H(_2)O</td>
<td>(NH(_4))(S(_2)O(_8))(20)</td>
<td>22:78</td>
<td>18.4</td>
<td>3.9</td>
<td>76.9</td>
<td>0.8</td>
<td>83(^a)</td>
</tr>
<tr>
<td>7</td>
<td>CH(_2)Cl(_2)</td>
<td>EtB(_3) (10)</td>
<td>32:68</td>
<td>25.6</td>
<td>7.0</td>
<td>63.5</td>
<td>4.1</td>
<td>50(^a)</td>
</tr>
<tr>
<td>8</td>
<td>CH(_2)Cl(_2)</td>
<td>BPh(_3) (10)</td>
<td>26:74</td>
<td>17.0</td>
<td>9.0</td>
<td>74.0</td>
<td>0.0</td>
<td>77(^a)</td>
</tr>
<tr>
<td>9</td>
<td>toluene</td>
<td>AlCl(_3) (10)</td>
<td>100:0</td>
<td>6.6</td>
<td>93.4</td>
<td>0.0</td>
<td>0.0</td>
<td>74(^a)</td>
</tr>
<tr>
<td>10</td>
<td>CH(_2)Cl(_2)</td>
<td>AlCl(_3) (10)</td>
<td>100:0</td>
<td>0.0</td>
<td>100.0</td>
<td>0.0</td>
<td>0.0</td>
<td>92(^a)</td>
</tr>
</tbody>
</table>

\(^a\) Evaluated by \(^1\)H NMR and \(^19\)F NMR.

\(^b\) Yield of isolated product.

a catalytic amount of AlCl\(_3\) (10 mol%) using CH\(_2\)Cl\(_2\) as solvent, yielding (E)-2\(\alpha\) as the sole product with excellent yield (entry 10).

In view of these results, we deduced that the optimum conditions for the hydrogermylation reaction of alkyne 1a to produce the corresponding trans-vinylgermane (E)-2\(\alpha\) in a complete regio- and cis-stereoselective manner is 1 mol of Ph\(_3\)GeH and 10 mol\% of AlCl\(_3\) in CH\(_2\)Cl\(_2\) at room temperature for 2 h.

The E- and Z-configurations of the two regioisomers 2\(\alpha\) and 2\(\beta\) were assigned based on the values of the coupling constant \(\int_{2}(C(\alpha)-F)\): for which \(\int_{2}(C(\alpha)-F)\) of the (Z)-isomer is higher than that of the (E)-isomer (Figure 2).\(^16,20\)

To investigate the scope and limitations of the AlCl\(_3\)-catalyzed hydrogermylation reaction, we next tested the hydrogermylation reaction of alkyne 1a using a less hindered organogermane compound such as Bu\(_3\)GeH. Remarkably, complete α-regioselectivity of the hydrogermylation of alkyne 1a was observed. However, the reaction was found to be highly but not completely stereoselective, because traces of the Z-stereoisomer were observed (E/Z = 91:9). Therefore, it seems that the size of the R group on R\(_3\)GeH is at the origin of this result. To further investigate the regiochemistry of vinylgermane 3, we then tested the radical hydrogermylation of alkyne 1a using Bu\(_3\)GeH in the presence of Et\(_3\)B as a radical initiator and CH\(_2\)Cl\(_2\) as solvent, providing a mixture of the four possible isomers (Z)-3\(\alpha\), (E)-3\(\alpha\), (Z)-3\(\beta\) and (E)-3\(\beta\) with the majority being the trans-addition product (Z)-3\(\beta\) (Scheme 2).

Another fluorinated α,β-acetylenic ester, ethyl 4,4,5,5,5-pentafluoropent-2-ynoate (1b),\(^13\) was then treated under the same conditions as those described above. The results obtained were very similar to those obtained in the case of alkyne 1a. The hydrogermylation of alkyne 1b using AlCl\(_3\) as catalyst in CH\(_2\)Cl\(_2\) and Ph\(_3\)GeH yields exclusively the cis-addition product (E)-4\(\alpha\) in 91% yield. Likewise, as observed in the case of alkyne 1a, there was a slight loss of stereoselectivity when triphenylgermane was substituted with the less bulky tributylgermane, but the regioselectivity remained complete. Similarly, radical hydrogermylation of

![Scheme 2 Hydrogermylation reaction](image-url)
alkyne 1b using Bu3GeH or Ph3GeH in the presence of Et3B was performed, yielding a mixture of α- and β-regioisomers in a ratio of ca. 33:67, respectively, with the majority of the trans-addition product (Z)-4β and (Z)-5β (Scheme 3).

![Scheme 3 Hydrogermylation of 1b using Ph3GeH and Bu3GeH](image)

To better understand the role of the fluorinated group of the alkyne in the orientation of the regioselectivity of the AlCl3-catalyzed hydrogermylation reaction, hydrogermylation of methyl 4,4-difluoro-4-phenylbut-2-ynoate (1c)25 using Ph3GeH was performed under the conditions described above (Scheme 4). Although the reaction gave the (E)-6α adduct as the major isomer, it was accompanied by the formation of the other three isomers in the proportions: (Z)-6α (7%), (E)-6α (55%), (Z)-6β (34%) and (E)-6β (4%).

![Scheme 4 AlCl3-catalyzed hydrogermylation of 1c using Ph3GeH](image)

It is worth mentioning that the regio- and stereochemistry for the vinylermanes 3, 4, and 6 were deduced from the 1H-F, 1JF-F and 1JC-F coupling patterns by following the analyses described above in case of vinylermane 2.

Despite the limited number of fluorinated alkynes used, it seems that the regioselectivity of this hydrogermylation reaction is also very dependent on the nature of the fluorinated group of the alkyne. This dependence may be related to the difference of the partial charges on sp-carbon atoms of the alkyne. To investigate this in greater detail, ab initio calculations were carried out (full minimization of the structure realized using the HF/6-311G* level of theory followed by a single-point calculation with the basic set DFT/B3-LYP/def-TZVP within Turbomole 7.2) to determine the partial charge of these two sp-carbon atoms (Scheme 5), thanks to the Natural Population Analysis approach.26 A larger difference on the partial charges (Δ = δC1-δC2) was observed in the cases of alkynes 1a and 1b than in alkyne 1c (Figure 3). Furthermore, changing a -CF3 (or -C2F5) group with a PhF2C induces a significant charge inversion on sp-carbon atoms. To further understand the origin of the regioselectivity of this hydrogermylation reaction by using AlCl3 as catalyst, a similar charge analysis was carried out on intermediates (1a', 1b' and 1c'). By looking at the partial charge of each carbocation, it seems that C3 of 1c' is less electrophilic than those of 1a' and 1b'. This may explain the higher regioselectivity observed in the case of alkynes 1a and 1b (Figure 3).

![Figure 3 Partial charges on the sp-carbon atoms](image)

By taking into consideration the charge distribution of these two sp-carbon atoms, a plausible ionic mechanism for the AlCl3-catalyzed cis hydrogermylation of fluorinated alkynes type 1 is shown in Scheme 5. The coordination of the ester-carbonyl group of alkynes of type 1 to AlCl3 produces the zwitterionic intermediate I, which is transformed into allenoate II through hydride transfer from Ph3GeH to the cationic center of I. Trapping of intermediate II with germium-type species occurs from the less hindered face, cis to H, thus providing the cis-hydrogermylation (E)-α products and regenerating the AlCl3 catalyst.

![Scheme 5 Plausible Mechanism for cis-hydrogermylation of fluorinated alkynes 1](image)
In summary, the AlCl3-catalyzed hydrogermylation reaction of ethyl propiolate bearing a perfluoroalkyl group can be achieved under very mild conditions. This reaction proceeds in a highly regio- and stereocontrolled manner, providing functionalized vinylgermane products with excellent yields. Studies are now under way to delineate the synthetic utility of these reagents and the results of these investigations will be reported in due course.

Most reagents were obtained from commercial sources and used as received. All reactions were carried out under inert atmosphere. Petroleum ether (PE) used had a boiling range 40–60 °C, CH2Cl2 was distilled from calcium hydride and stored under Argon. Thin-layer chromatography (TLC) was performed on Merck 60F254 plates. Column chromatography was carried out with Merck silica gel 60 (0.040–0.063 mm, 230–400 mesh). All 1H, 13C, and 19F NMR spectra were recorded with a 300 MHz Bruker Avance FT NMR spectrometer (300 MHz, 75 or 282 MHz, respectively). All chemical shifts are given as δ values (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The coupling constants J are reported in Hertz (Hz). Electrospray ionization high-resolution mass spectrometry experiments (HRMS) were performed with a hybrid tandem quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, U.K.) operated in positive mode.

AlCl3-Catalyzed Hydrogermylation Reaction: Synthesis of (E)-a Adduct; General Procedure A

Alkyne 1a (143 mg, 0.86 mmol) was placed in a vial containing a magnetic stirring bar. AlCl3 (12 mg, 0.09 mmol, 10 mol%) in CH2Cl2 (0.5 mL) was added to the vial. The vial was sealed with a Teflon-coated silicon rubber septum, evacuated and filled with argon. The reaction mixture was left for 3 hours under agitation at r.t. then hexane was added and the mixture was allowed to warm to r.t. then hexane was added and the mixture was filtered through Celite. The solvent was evaporated under vacuum and column chromatography through silica gel afforded the purified (E)-2a-isomer (290 mg, 92%) with complete regio- and stereoselectivity.

Radical Hydrogermylation using BEt3: Synthesis of Mixture of Isomers (E)-β, (Z)-β, (E)-α, (Z)-α; General Procedure B

Triethylborane (6 mg, 0.1 equiv, 0.06 mmol), Bu3GeH (177 mg, 1.2 equiv, 0.72 mmol) and CH2Cl2 (0.4 mL) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon-coated silicon rubber septum, evacuated and filled with argon. Alkyne 1a (100 mg, 1 equiv, 0.60 mmol) was added slowly to the reaction mixture. The reaction mixture was left for 3 hours under agitation at r.t. then the solvent was evaporated under vacuum. Column chromatography through silica gel using PE as eluent afforded the four isomers (247 mg, 50% overall yield).

Yield: 92%; white solid; mp 85–86 °C.


(E)-Ethyl 4,4,4-Trifluoro-2-(tributylgermyl)but-2-enoate [(E)-2β]

(E)-2β was obtained as a mixture with (E)-2α by following general procedure A.

(E)-Ethyl 4,4,4-Trifluoro-3-(tributylgermyl)but-2-enoate [(E)-3β]

(E)-3β was obtained as a mixture with (E)-3α by following general procedure A.

(E)-Ethyl 4,4,4-Trifluoro-2-((triphenylgermyl)but-2-enoate [(E)-2α]

(E)-2α was obtained as the sole product by following general procedure A.

(Z)-Ethyl 4,4,4-Trifluoro-2-((triphenylgermyl)but-2-enoate [(Z)-2α]

(Z)-2α was obtained as a mixture with (Z)-3α by following general procedure B.

(E) (Z)-Ethyl 4,4,4-Trifluoro-3-((triphenylgermyl)but-2-enoate [(E)-3β] (Z)-3β was obtained as a mixture with the other three isomers by following general procedure B.

(E)-Ethyl 4,4,4-Trifluoro-2-((tributylgermyl)but-2-enoate [(E)-2β]

(E)-2β was obtained as a mixture with the other three isomers by following general procedure B.

(Z)-Ethyl 4,4,4-Trifluoro-3-((tributylgermyl)but-2-enoate [(Z)-2α]

(Z)-2α was obtained as a mixture with (Z)-3α by following general procedure B.
(Z)-3a was obtained as a mixture with (E)-3a by following general procedure A.

1H NMR (CDCl3, 300 MHz): δ = 6.61 (q, J=8.5 Hz, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 1.38–1.28 (m, 12 H).

13C NMR (CDCl3, 75 MHz): δ = 166.3, 145.2 (t, J=4.8 Hz), 135.6 (6C), 132.7 (3C), 130.1 (3), 128.7 (6C), 126.8 (t, J=23.4 Hz), 118.8 (qt, J=252.8 Hz, 38.8 Hz), 61.3, 13.8.

19F NMR (CDCl3, 282 MHz): δ = –82.76 (t, J=1.8 Hz, CF3), –113.91 (q, J=1.8 Hz, CF3).

Yield: 84%; colorless oil.

5Z-3b was obtained as a mixture with the other three isomers by following general procedure B.

1H NMR (CDCl3, 300 MHz): δ = 6.50 (t, J=13.3 Hz, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 1.38–1.25 (m, 18 H), 0.97–0.86 (m, 12 H).

19F NMR (CDCl3, 282 MHz): δ = –82.95 (t, J=2.2 Hz, CF3), –113.95 (q, J=2.2 Hz, CF3).


(2Z,4E)-4b was obtained as a mixture with the other three isomers by following general procedure B.

1H NMR (CDCl3, 300 MHz): δ = 7.66–7.70 (m, 15 H), 6.66 (t, J=1.7 Hz, 1 H), 4.28 (q, J = 7.1 Hz, 2 H), 0.86 (t, J=7.1 Hz, 3 H).

19F NMR (CDCl3, 282 MHz): δ = –82.11 (t, J=2.2 Hz, CF3), –102.12 (q, J=2.2 Hz, CF3).

Yield: 84%; colorless oil.
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Supporting Information

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