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Stereodivergent Hydrogermylations of α-Trifluoromethylated Alkynes and Their Applications in Cross-Coupling Reactions

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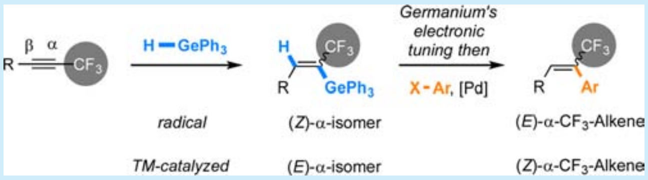
Supporting Information

ABSTRACT: The hydrometalation of alkynes with group 14 elements such as tin- or silyl hydrides is a classical transformation in organic synthesis. Strangely, among the group 14 elements, the use of germanium hydrides is rarely seen. Two efficient, stereodivergent, and broadly applicable routes to (Z)- and (E)-α-CF_3-vinylgermanes by regio- and stereoselective hydrogermylation of α-trifluoromethylated alkynes under radical or transition-metal-catalyzed conditions are reported. Furthermore, we demonstrate that the resulting stereodefined fluorinated building blocks are remarkable cross-coupling partners, provided that the vinylgermane is appropriately tuned electronically, as demonstrated by the synthesis of trisubstituted (Z)- and (E)-α-trifluoromethylated alkenes.



Due to the unique properties of fluorine, the selective introduction of fluorinated building blocks in a controlled fashion is central to many areas of chemistry, from medicinal to material.[1] Along these lines, our interests have been focused on the synthesis of fluorinated analogs of rare natural products for the study of the biology that they impart. Indeed, the introduction of fluoroalkyl groups on natural products can dramatically improve their biological effects, and in this regard, a remarkable example is the evolution of the potent antimitotic and antineoplastic agents, epothilones.[2] The introduction of a CF_3 motif on the C12−C13 π-system of certain epothilone analogues, such as Fludelone and 17-iso-oxazole-Fludelone, leads to an improved therapeutic index and properties such as potency, solubility, stability, and duration of action (Figure 1A). Surprisingly, the selective introduction of (E)- and (Z)-trifluoromethylated alkenes during the structural editing of natural products is still a daunting task.

The few synthetic strategies enabling such an operation are olefination reactions,[3] transition-metal-mediated trifluoromethylations of prefunctionalized alkenes,[4] and direct sp^2 C−H bond functionalization.[5]

However, limited scope and stereoselectivity issues are often encountered and there is a strong need for robust methods for the synthesis of trifluoromethylated alkenes. An attractive option that could provide an efficient approach to such motifs would rely on a hydrometalation/cross-coupling sequence from α-CF_3-alkynes, readily available and remarkably polarized alkynes whose reactivity has been understudied.[6] Indeed, provided that high levels of regio- and stereoselectivity could be attained during the hydrometalation and that the metal introduced could be readily used for further functionalization by cross-coupling reactions, this could represent a major step forward toward the development of a general route to trifluoromethylated alkenes.

Although previous results from the Kobayashi, Hiyama, and Konno groups demonstrated the feasibility of the hydrometalation (hydrosilylation, borylation, alumination, cupration, and stannylation) of α-CF_3-alkynes, most examples are limited to certain classes of substrates (i.e., aryl-substituted α-CF_3-alkynes) and still lack generality.[6,7] In addition, the resulting fluorinated substrates cannot always participate in cross-coupling reactions.[8] A general regio- and stereoselective hydrometalation of α-CF_3-alkynes using a nontoxic yet reactive metal is therefore still an unmet challenge. As a solution to tackle this challenge, we envisioned that a hydrogermylation reaction, whose stereoselectivity could be tuned depending on the conditions used, could potentially provide an efficient and divergent route to α-CF_3-vinylgermanes **2** and **3**, substrates that could be further used in cross-coupling reactions after germanium's electronic tuning (Figure 1B).

Germanium is a group 14 element between silicon and tin whose synthetic chemistry is still in its infancy.[9a] Also slightly more expensive than tin derivatives, organogermanium derivatives are nontoxic and have a much improved stability.[9b]

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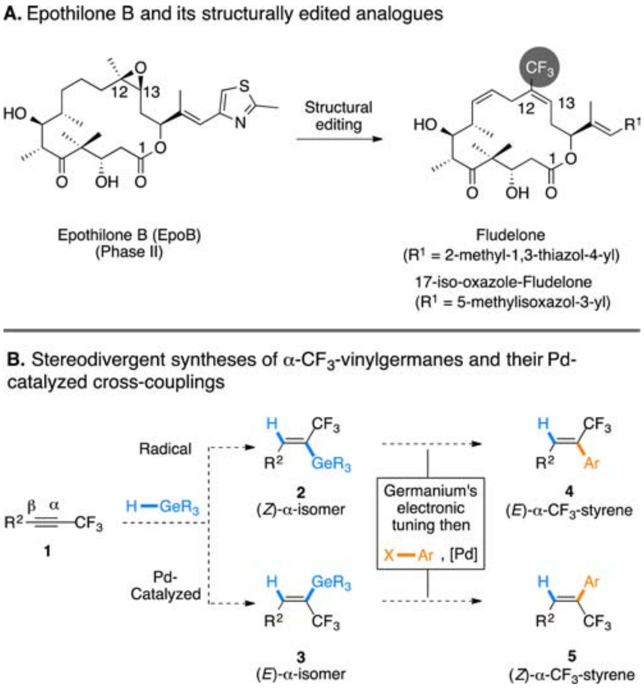


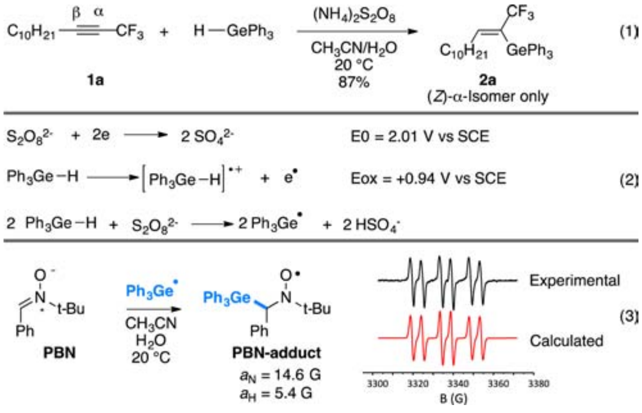
Figure 1. Relevance of stereodefined CF_3-alkenes in natural product editing and proposed strategy.

Organogermanium hydrides have been used for radical and transition-metal-catalyzed hydrogermylation of alkenes and alkynes since the mid 1950s, but these transformations still suffer from serious limitations such as low regio- and stereoselectivities and limited functional group tolerance.[10] Since the initial report of Gilman in 1957,[11] only a handful of reports have been published on radical hydrogermylation of π-systems, mainly by the group of Oshima.[12] Besides the radical mechanistic framework, transition-metal-catalyzed hydrogermylation of terminal alkynes has been more extensively studied since the 1970s, with catalysts based on rhodium,[13a−c] platinum,[13d,e] palladium,[13f] ruthenium,[13g] or iron.[13h] Finally, one last class of hydrogermylation that is worth mentioning is the Gevorgyan Lewis acid catalyzed hydrogermylation of terminal alkynes.[13i] This rapid overview of the literature highlights the lack of studies concerning the stereoselective hydrogermylation of alkynes in general and more specifically of α-fluorinated alkynes, despite its potential.

Aiming to identify stereocomplementary hydrogermylation methods, we elected to use α-trifluoromethylated alkyne **1a** as a model substrate.[14] It was rapidly discovered that peroxydisulfate[15] was an inexpensive radical initiator in the hydrogermylation of **1a** using triphenylgermane, in aqueous acetonitrile at room temperature under an air atmosphere (Scheme 1). The α-trifluoromethylvinylgermane **2a** was obtained in 87% isolated yield as a unique (*Z*)-isomer (as determined by ^{19}F NMR and NOE)[6] in line with the exquisite selectivity observed in related radical hydrosilylations of terminal alkynes.[16,17]

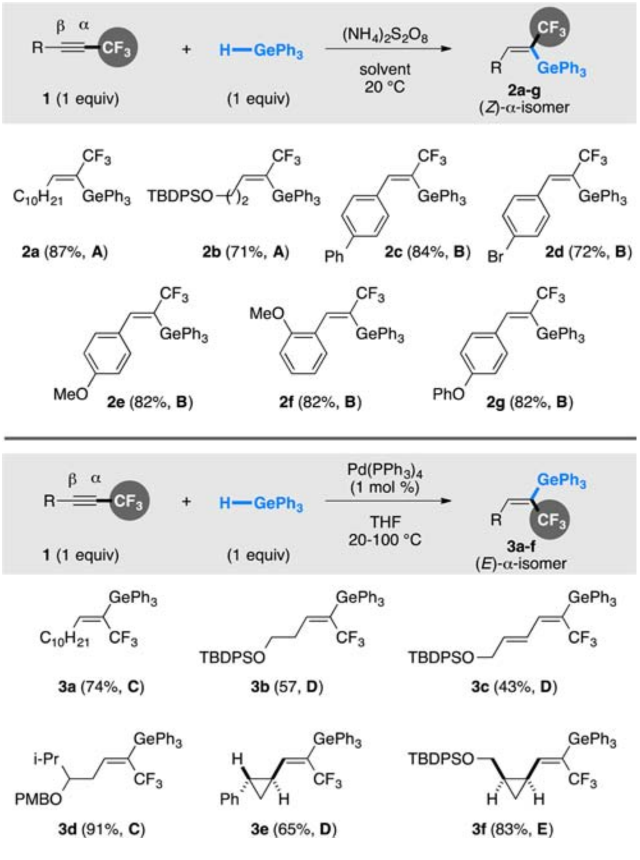
The oxidation potentials of peroxydisulfate and triphenyl germane were measured by cyclic voltammetry and are consistent with an easy oxidation of the latter, leading to triphenylgermyl species (Scheme 1, eq 2). The intermediacy of this oxidatively generated triphenylgermyl radical was proven using spin trapping experiments with phenyl *tert*-butylnitrone, as can be seen in Scheme 1, eq 3.[17]

Scheme 1. Radical Hydrogermylation of CF_3-Alkynes



This practical radical hydrogermylation proved to be quite general since both alkyl and aryl substituted α-trifluoromethylated alkynes **1a−g** led to good to excellent yields of the corresponding (*Z*)-α-trifluoromethylvinylgermanes **2a−g** in acetonitrile (Method A) or DMF (Method B) (Scheme 2). These were the sole regio- and stereoisomers of the crude reaction mixture as determined by ^{19}F NMR. Primary silyl ether **2b**, diarylether **2g**, alkyl aryl ether **2e** and **2f**, and aromatic bromide **2d** were stable under these oxidative conditions. Having in hand a straightforward access to (*Z*)-α-trifluoromethylvinylgermanes **2**, we next focused on a stereocomple-

Scheme 2. (*Z*)- and (*E*)-Selective Hydrogermylation of CF_3-Alkynes[a]

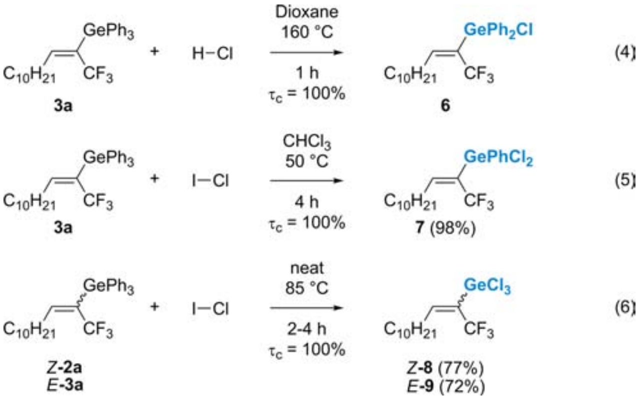


[a] Solvent, temp: **A** = CH_3CN/H_2O, 20 °C; **B** = DMF, 20 °C; **C** = THF, 20 °C; **D** = THF, 50 °C; **E** = THF, 100 °C for 1−12 h.

mentary route to the (*E*)-isomer. Investigation of different transition-metal-catalyzed hydrogermylation reactions led to the selection of Pd(PPh_3)$_4$ at a low loading (1 mol %) in THF at 20, 50, or 100 °C (methods C, D, and E respectively). Much to our delight, the ^{1}H and ^{19}F NMR spectra of the crude hydrogermylation of **1a** revealed a quantitative formation of the (*E*)-*α*-trifluoromethylvinylgermane **3a**, resulting from a regio- and stereoselective *cis*-addition pathway (67% isolated yield). No (*Z*)-isomer **2a** was observed, and less than 5% of the *β*-isomer was detected. The scope of this palladium-catalyzed hydrogermylation was next studied with diversely substituted *α*-trifluoromethylated alkynes **1**.[18] Once again, silyl ethers **3b**, **3c**, and **3f** and *p*-methoxybenzyl ether **3d** were tolerated. Worthy of note is the selective access to the (*E*,*E*)-trifluoromethylated dienylgermane **3c**, although with only a moderate yield (43%). 1,2-*trans*- and *cis*-Propargylic cyclopropanes **1j** and **1k** led to vinyl germanes **3e** and **3f** at higher temperature (50 and 100 °C respectively), without any traces of the corresponding allenes that could arise from a competitive ring opening of the cyclopropyl motif.

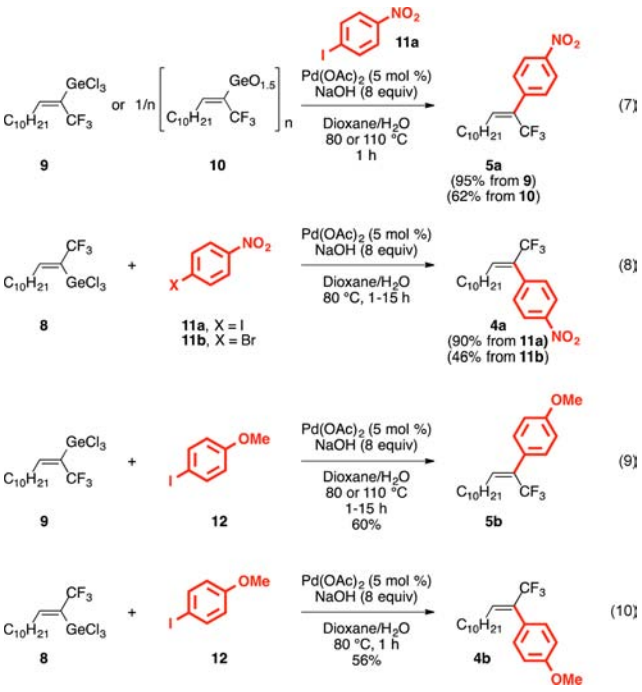
These two stereoselective hydrogermylation reactions of alkynes thus give access to unique fluorinated building blocks for cross-coupling reactions, provided that the electron deficiency of the germanium atom is finely tuned.[19] With this goal in mind, it was discovered that the mono-, di-, and trichlorogermanes **6**–**9** coud be selectively and very cleanly obtained upon exposure of **2a** and **3a** to the appropriate electrophiles (Scheme 3, eqs 4–6).[20,21] Indeed, these rare *ipso*-proto/iododegermylations of the triphenylgermyl motif are an illustration of both the *β*-stabilizing effect of germanium, which is known to increase while descending column 14, and the electron deficiency of the trifluoromethyl-substituted alkenes. The sp^2-trichlorogermane **9** can also be converted into the bench-stable sesquioxide **10**[21] upon reaction with aqueous ammonia,[22] the germane sesquioxides being also reactive nucleophilic motifs in palladium-catalyzed cross-coupling reactions.[23]

Scheme 3. Electronic Tuning of *α*-CF_3-Vinylgermanes



With this set of vinylgermanes in hand, we next investigated their reactivity in palladium-catalyzed arylation reactions, under the conditions reported by Fugami and Kosugi (Scheme 4, eqs 7–10).[24] The reactivity of the sp^2-trichlorogermanes in cross-coupling reactions can be traced back to their easy hydrolysis into the corresponding nucleophilic hydroxygermanes (and ate-complexes) upon exposure to traces of water.[19] The mono- and dichlorogermanes **8** and **9** were not reactive cross-coupling partners in the presence of Pd(OAc)$_2$ (5 mol %) and sodium hydroxide (8 equiv) in aqueous dioxane at 80–110 °C, even with activated iodo-aromatics.[17] In sharp contrast, the cross-couplings of the (*Z*)- and (*E*)-trichlorogermanes **8** and **9** as well as sesquioxide **12** with aryl iodide **11a** delivered in good to excellent yields the corresponding *α*-trifluoromethylated styrenes **5a** and **4a**, as single isomers (Scheme 4, eqs 7 and 8, respectively). Use of the corresponding aryl bromide **11b** led to a halving of yield (46% vs 90%, Scheme 4, eq 8). Finally, electron-rich aryl iodide **12** was successfully cross-coupled with the (*E*)- and (*Z*)-trichlorogermanes **9** and **8**, leading to the *α*-trifluoromethylated styrenes **5b** and **4b** in good yields, still as single stereoisomers (Scheme 4, eqs 9 and 10).

Scheme 4. Pd-Catalyzed Arylations of *α*-CF_3-Vinyltrichlorogermanes and Sesquioxide



In summary, we have developed two efficient stereocomplementary routes to (*Z*)- and (*E*)-*α*-trifluoromethylvinylgermanes by regio- and stereoselective hydrogermylation of *α*-trifluoromethylated alkynes under radical and transition-metal-catalyzed conditions. These unique fluorinated building blocks are efficient precursors of nucleophilic components in palladium-catalyzed cross-couplings with aryl halides, as demonstrated by the totally stereoselective synthesis of trisubstituted (*Z*)- and (*E*)-*α*-trifluoromethylalkenes. Current studies aiming at the cross-coupling of other sp^2 and sp electrophiles are in progress in our laboratory and will be communicated in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental procedures, spectroscopic characterizations and copies of NMR are reported in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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