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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b09851 • Publication Date (Web): 29 Nov 2018

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Radical Germylzincation of α-Heteroatom-Substituted Alkynes

Karen de la Vega-Hernández, Elise Romain, Anais Coffinet, Kajetan Bijouard, Geoffrey Gontard, Fabrice Chemla, Franck Ferreira, Olivier Jackowski, and Alejandro Perez-Luna*

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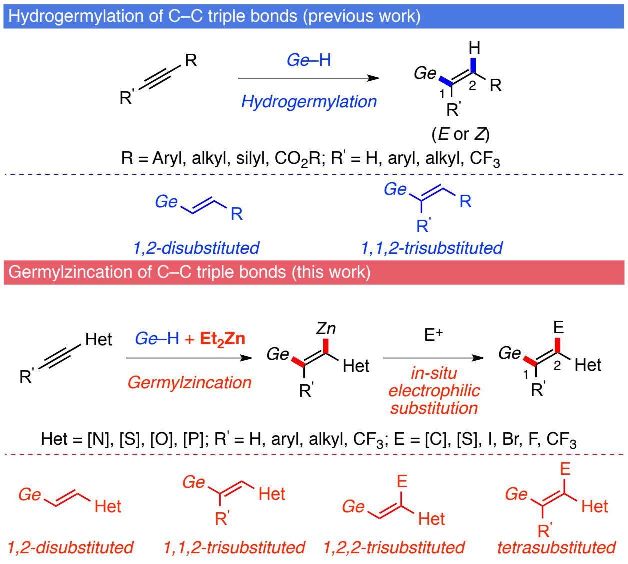
ABSTRACT: The regio- and stereoselective addition of germanium and zinc across the C–C triple bond of nitrogen-, sulfur-, oxygen-, and phosphorous-substituted terminal and internal alkynes is achieved by reaction with a combination of R_3GeH and Et_2Zn. Diagnostic experiments support a radical-chain mechanism and the β-zincated vinylgermanes that show exceptional stability are characterized by NMR spectroscopy and X-ray crystallography. The unique feature of this new radical germylzincation reaction is that the $C(sp^2)$–Zn bond formed remains available for subsequent *in situ* Cu(I)- or Pd(0)-mediated C–C or C–heteroatom bond formation with retention of the double bond geometry. These protocols offer a modular access to elaborated tri- and tetrasubstituted vinylgermanes decorated with heteroatom substituents β to germanium that are useful for the preparation of stereodefined alkenes.

INTRODUCTION

Vinylgermanes[1] are attractive synthetic building blocks that offer specific features such as increased stability towards protonolysis,[2] facile halodegermylation[3] or low toxicity,[4] which make them useful when limitations are met with the more popular group 14 homologues vinylsilanes and vinylstannanes.[5] Hence, the preparation of vinylgermanes is a field of intense ongoing research. A number of approaches have proved suitable for the preparation of vinylgermanes,[1c] including electrophilic substitution of vinylmetals with halogermanes,[3b,6] Pd-catalyzed germylation of vinyl halides,[7] hydro-[3a,8] or carbometalation[9] of alkynylgermanes, radical substitution of vinylsulfides,[10a] -stannanes,[10a] or -sulfones,[10b] alkene germylation through coupling with hydrogermanes[11] or with vinylgermanes,[12] olefination of acylgermanes,[13] or domino arylgermylation of oxanorbornadiene / retro-Diels-Alder.[14] Yet, the direct synthesis of vinylgermanes from alkynes by carbon-germanium bond-forming addition reactions represents the most straightforward approach and has received the greatest attention. The hydrogermylation of alkynes with hydrogermanes has been disclosed through thermal or microwave-activated,[15] radical,[16] transition-metal-catalyzed,[3a,8d,16e,17] as well as main-group Lewis-acid-catalyzed addition processes.[18] These protocols offer high levels of regio- and stereocontrol, but a shared fundamental limitation is that they cannot provide access to derivatives having two substituents distal to the position of the alkene germyl group (Scheme 1, top). Furthermore, only some of the aforementioned synthetic alternatives have been implemented for this purpose,[6,9,10,13b] and they rely on more elaborated starting materials and are not wide-in-scope. Thus, there is no direct and general solution available for the regio- and stereoselective preparation of 1,2,2-trisubstituted or tetrasubstituted vinylgermanes.

To satisfy this demand, alkyne germylmetalation, i.e. the 1,2-addition of germanium–metal bonds across the carbon–carbon triple bond of alkynes, is particularly appealing as it establishes in a single synthetic operation a $C(sp^2)$–Ge bond and a $C(sp^2)$–metal bond. The newly formed reactive bond can be used as linchpin for subsequent C–C bond formation in one pot following electrophilic substitution. However, in sharp contrast with the related silylmetalation and stannylmetalation reactions that are prevalent approaches for the preparation of polysubstituted vinylsilanes[19] and vinylstannanes,[20] germylmetalation reactions are almost unknown. The reaction between (trimethylgermyl)copper and a terminal alkyne was reported to be low yielding.[21] Also, the germylcupration of terminal acetylenes with (triethylgermyl)- and (triphenylgermyl)cuprates was disclosed:[22] excellent *cis* stereoselectivity was observed, but regiocontrol was only achieved with the triphenylgermyl reagents. In that case however, the addition was found to be reversible and in favor of the starting materials; hence vinylgermane formation only proceeded in the presence of a proton donor and the $C(sp^2)$–Cu bond formed was not available for subsequent elaboration.[23] It is also worthy of mention that protocols for the related alkyne germylstannation were developed using the oxidative addition chemistry of Ge–Sn compounds.[24–26] Nonetheless, following this approach, subsequent elaboration of the $C(sp^2)$–Sn bond required an additional synthetic step.[27]

Scheme 1. Synthesis of Vinylgermanes from Alkynes with C–Ge bond formation (*Ge* = triorganogermyl)



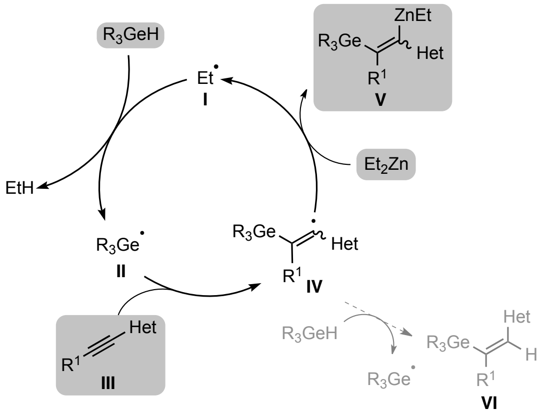
Here we focus on α-heteroatom-substituted alkynes, a substrate class that has not been considered previously for the above-described methods and that would deliver valuable heteroatom-substituted alkenes.[28] We describe the regio- and stereoselective germylzincation of both terminal and internal nitrogen-, oxygen-, sulfur- and phosphorus-substituted alkynes by reaction with a combination of a hydrogermane and Et_2Zn (Scheme 1, bottom). Upon hydrolysis of the $C(sp^2)$–Zn bond or *in situ* Cu(I)- or Pd(0)-mediated functionalization, this method gives access to a variety of original di-, tri- and tetrasubstituted vinylgermanes. As part of this work, we also demonstrate the synthetic potential of this construction of orthogonally 1,2-dimetalated alkenes.

Our idea, shown in Scheme 2, was to develop a radical approach similar to the one we recently applied to obtain the silylzincation of terminal α-heteroatom-substituted alkynes using a combination of $(Me_3Si)_3SiH$ and Et_2Zn.[29] We reasoned that germanium-centered radicals **II**, produced by H-atom transfer between hydrogermanes and ethyl radical (**I**) (**I→II**), should add readily across the C–C triple bond of α-heteroatom-substituted alkynes **III** to provide regioselectively α-heteroatom-substituted vinylic radicals **IV** (**III→IV**). Radicals **IV** would then react with Et_2Zn by homolytic substitution (S_H2) at the zinc atom (**IV→V**) to afford β-zincated vinylgermanes **V** along with ethyl radical **I** that would propagate the radical chain. For such a process to be possible, radical **IV** would have to undergo Zn-atom transfer (**IV→V**) faster than competitive H-atom transfer from R_3GeH (**IV→VI**). Otherwise, radical hydrogermylation[16] would be the main reaction outcome and the Zn functionality would be lost.

Estimation of the rate coefficients for each elementary step involved provided support for the feasibility of this radical chain, as they were all expected to be well above 10^2 M^{-1} s^{-1}, the commonly accepted lower limit for a radical chain to propagate in dilute solutions.[30] Triaryl- and trialkylgermanes undergo H-atom abstraction from alkyl radicals with rate constants in the range of 10^5–10^6 M^{-1} s^{-1} at ca. 30 °C.[31] Moreover, it is also important to emphasize here that the rate for the addition of the ethyl radical across alkynes with α-heteroatom substituents should be lower than ~10^5 M^{-1} s^{-1}, which is the rate for the addition of alkyl radicals across propiolates (terminal alkynes with a strong electron-withdrawing substituent):[32] thus, direct ethyl radical addition leading to carbozincation products should be avoided. The rate constant for the addition of germanium-centered radicals across alkynes has not been determined,[32] but it should be of the same order of magnitude (though lower) than that for additions of silyl-centered radicals[33] (1 x 10^8 M^{-1} s^{-1} at 27 °C for the addition of the triethylsilyl radical across phenylacetylene).[32] While little is known about the rate for the reaction between vinyl radicals and Et_2Zn, our previous work on radical silylzincation demonstrates that for α-heteroatom-substituted vinylic radicals (**IV**), the rate for S_H2 at the zinc atom is suitable for chain propagation and can outcompete H-atom transfer from $(Me_3Si)_3SiH$.[29] Given that the rates for radical H-abstraction are in comparable ranges for R_3GeH and for $(Me_3Si)_3SiH$,[31] a similar situation was expected here.

Finally, regarding the initiation of the radical chain (not shown in the scheme), we surmised that it could occur, even in the absence of deliberately added radical initiators, through several pathways, including spontaneous-[17b,34] or light[35]-induced homolysis of the Ge–H bond (as for the hydrogermylation reactions)[36] or oxidation of diethylzinc by traces of molecular oxygen.[37, 38]

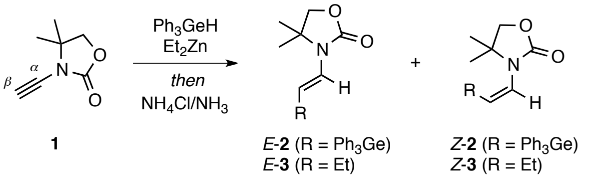
Scheme 2. Anticipated Radical Approach to the Germylzincation of α-Heteroatom-Substituted Alkynes



RESULTS AND DISCUSSION

We commenced our study by investigating the germylzincation of model terminal ynamide **1** with Ph_3GeH, a well-established radical hydrogermylating reagent that is commercially available and easy-to-handle (Table 1). The initial conditions involving 1.3 equiv of hydrogermane and 3.0 equiv of Et_2Zn at 0 °C in *n*-hexane, led to the exclusive formation of β-germylenamide **2** as an E/Z = 30:70 mixture of isomers, but the reaction was not complete and only ~ 60% of **1** was consumed (Entry 1). In fact, competitive deprotonation of **1** by Et_2Zn as well as direct hydrogermylation delivering *Z*-**2** hampered the germylzincation process. A survey of other solvents was then carried out. While no significant improvement was observed in CH_2Cl_2 and Et_2O, reactions in benzene and methyl *tert*-butyl ether (MTBE) afforded improved conversion (~ 80%). The stereoselectivity was only modest but, by contrast with the reaction in *n*-hexane, often in favor of the *E* isomer. Furthermore, in MTBE, competitive carbozincation giving **3** was also observed. Eventually, full conversion and total stereocontrol, also in favor of the *E* isomer, were obtained using Me-THF and THF. Nevertheless, carbozincation of **1** occurred to some extent with the more hindered ether, and a better yield in **2** (87% *vs* 64%) was obtained in THF. With lower amounts of Et_2Zn (1.8 or 1.2 equiv), the reaction also took place with high conversion and exclusive formation of **2**, albeit with lower stereocontrol.

Table 1. Optimization of the Germylzincation of Ynamide 1

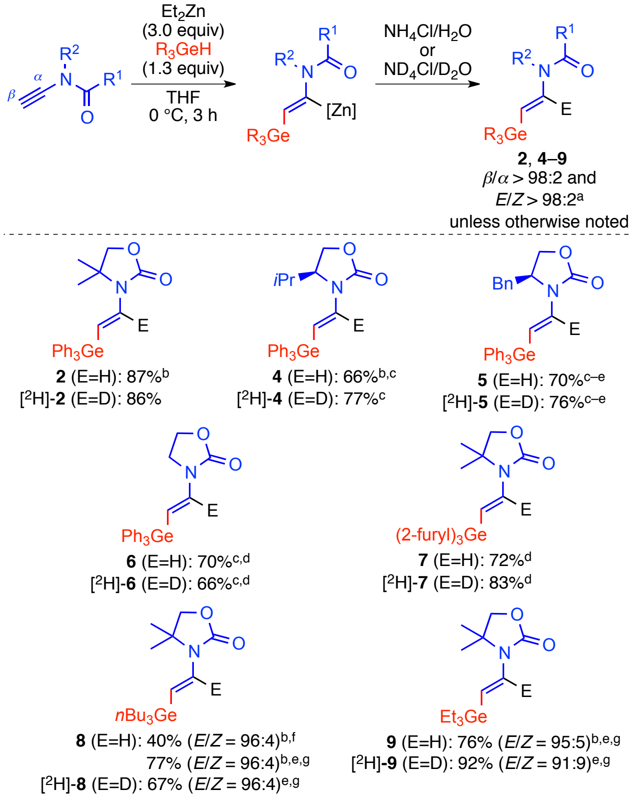


Entry	Solvent[a]	Et_2Zn [equiv]	Conversion[b,c] (**2**/**1**)	d.r. **2** (*E*/*Z*)[c]	Yield **2** (%)[d]
1	*n*-hexane[e]	3.0	62:38	30:70	nc[f]
2	CH_2Cl_2	3.0	50:50	70:30	37
3	Et_2O	3.0	54:46	48:52	29
4	benzene	3.0	85:15	57:43	nc[f]
5	MTBE	3.0	80:20	68:32	62[g]
6	Me-THF	3.0	>99:1	98:2	64[h]
7	THF	3.0	>99:1	>98:2	87
8	THF	1.8	>99:1	90:10	nc[f]
9	THF	1.2	89:11	76:24	nc[f]

[a] Reaction conditions: Ph_3GeH (1.3 equiv), 0 °C, 3 h unless otherwise stated. [b] Only *β*-germylated regioisomers were detected. [c] Determined by ^1H NMR prior to purification. [d] Combined yield of isolated diastereomers. [e] Reaction time = 6 h. [f] Not calculated. [g] 6% of **3** was observed. [h] 10% of **3** was observed.

The scope of this new germylzincation reaction of terminal ynamides was next considered (Scheme 3). Modification of the substitution pattern *α* to the nitrogen atom of the oxazolidinone ring was well tolerated and *β*-germylenamides **4–6** were isolated in good yields and as single *E* isomers.[39] Here however, small amounts (10–12%) of carbozincation adducts were detected in the crude. Other hydrogermanes were also used. Trifurylgermane[40] reacted smoothly to provide stereopure *E*-**7** in 72% yield. With nBu_3GeH, the conversion (50%) was not complete and product **8** was obtained in a lower 40% yield along with 10% of the carbozincation adduct (**3**). In this case, the rate coefficient for the reaction between alkyl radicals and the hydrogermane is around one order of magnitude lower than for triarylgermanes:[41] this makes ethyl radical addition more competitive and the propagation of the radical chain (Scheme 2, **I→II**) less efficient. Nevertheless, with higher amounts of hydrogermane (2.0 equiv) and longer reaction times, nBu_3GeH and Et_3GeH led respectively to **8** and **9** in high yields with very high (≥ 95:5) stereoselectivities, and no ethylzincation was observed.

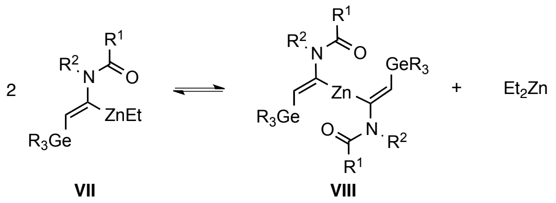
Scheme 3. Reaction Scope for the Germylzincation of Terminal Ynamides



[a] Measured by ^1H NMR prior to purification. [b] Reaction was quenched with NH_4Cl/NH_3. [c] 10–12% of Et addition was detected. [d] CuTC (1.0 equiv) was added before the reaction quench. [e] 16 h reaction time. [f] 10% of **3** was formed. [g] R_3GeH (2.0 equiv).

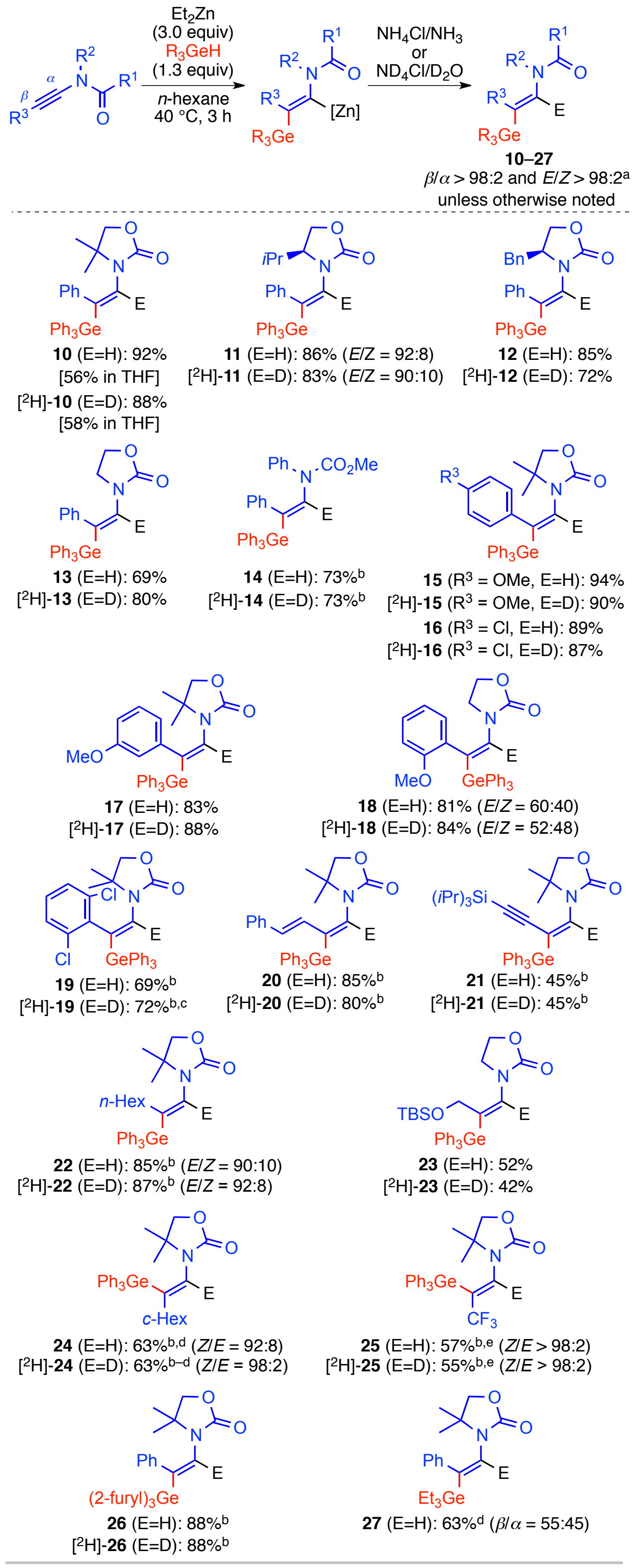
The formation of vinylzinc intermediates upon reaction with R_3GeH / Et_2Zn under the developed conditions was studied systematically by deuterium labeling and D-incorporation > 95% at the *α*-position was observed in every case (Scheme 3). It must be noted however that these experiments were complicated by the remarkably high stability towards hydrolysis of the $C(sp^2)$–Zn bond of divinylzinc species **VIII** (Scheme 4), likely formed by Schlenk equilibration of the intermediates **VII** arising from germylzincation (*vide infra*). In some cases, organometallic species **VIII** reacted only partially with ND_4Cl/D_2O[42] or MeOD, leading to flawed D-incorporation values and significant amounts of **VIII** were recovered in the crude even after extended exposure to aqueous solutions or after column chromatography on silica gel! Efficient deuteriodemetalation of intermediates **VIII** was nevertheless achieved upon addition of CuTC (Copper(I)-thiophene-2-carboxylate) prior to the reaction quench and reliable D-labeling data could be collected. Similar quench conditions (CuTC / NH_4Cl / H_2O) were also used in the preparation of non-labeled **5, 6** and **7**.

Scheme 4. Schlenk Equilibrium of *α*-Zincated *β*-Germylenamides



Importantly, the germylzincation reaction was also found to be well suited for internal ynamides (Scheme 5).

Scheme 5. Reaction Scope for the Germylzincation of Internal Ynamides



10–27
$\beta/\alpha > 98:2$ and $E/Z > 98:2$[a] unless otherwise noted

10 (E=H): 92% [56% in THF]
[^{2}H]-**10** (E=D): 88% [58% in THF]

11 (E=H): 86% (E/Z = 92:8)
[^{2}H]-**11** (E=D): 83% (E/Z = 90:10)

12 (E=H): 85%
[^{2}H]-**12** (E=D): 72%

13 (E=H): 69%
[^{2}H]-**13** (E=D): 80%

14 (E=H): 73%[b]
[^{2}H]-**14** (E=D): 73%[b]

15 (R^3 = OMe, E=H): 94%
[^{2}H]-**15** (R^3 = OMe, E=D): 90%
16 (R^3 = Cl, E=H): 89%
[^{2}H]-**16** (R^3 = Cl, E=D): 87%

17 (E=H): 83%
[^{2}H]-**17** (E=D): 88%

18 (E=H): 81% (E/Z = 60:40)
[^{2}H]-**18** (E=D): 84% (E/Z = 52:48)

19 (E=H): 69%[b]
[^{2}H]-**19** (E=D): 72%[b,c]

20 (E=H): 85%[b]
[^{2}H]-**20** (E=D): 80%[b]

21 (E=H): 45%[b]
[^{2}H]-**21** (E=D): 45%[b]

22 (E=H): 85%[b] (E/Z = 90:10)
[^{2}H]-**22** (E=D): 87%[b] (E/Z = 92:8)

23 (E=H): 52%
[^{2}H]-**23** (E=D): 42%

24 (E=H): 63%[b,d] (Z/E = 92:8)
[^{2}H]-**24** (E=D): 63%[b–d] (Z/E = 98:2)

25 (E=H): 57%[b,e] (Z/E > 98:2)
[^{2}H]-**25** (E=D): 55%[b,e] (Z/E > 98:2)

26 (E=H): 88%[b]
[^{2}H]-**26** (E=D): 88%[b]

27 (E=H): 63%[d] (β/α = 55:45)

[a] Measured by ^{1}H NMR prior to purification. [b] 16 h reaction time. [c] CuTC (1.0 equiv) was added before the reaction quench. [d] 2.0 equiv R_3GeH. [e] 13% of Et addition and 9% of an α-isomer were detected.

For this substrate class, the best conditions for the reaction with Ph_3GeH / Et_2Zn involved using *n*-hexane as solvent at 40 °C. Here, direct hydrogermylation did not interfere with the germylzincation process, and β-germylenamide *E*-**10** was obtained from the parent Ph-substituted ynamide in 92% yield with β-regioselectivity and *cis*-stereoselectivity. The same exquisite regio- and stereoselectivity was observed at lower temperatures and/or in THF, but conversion of the starting material was not complete.

Modification of the nitrogen substituent was also well tolerated here. *E*-enamides **11**–**13** having different oxazolidinone rings were obtained in 69-86% yields from the corresponding cyclic ynamides. Importantly and by contrast with the terminal ynamides derived from the same oxazolidinones, competing ethyl radical addition was not observed, what is consistent with the lower rate coefficient for the addition of alkyl radicals to disubstituted alkynes than to monosubstituted alkynes.[32] Moreover, enamide **14** having an acyclic carbamate was produced, with full regio- and stereoselectivity, in 73% yield. The *E* configuration of products **12** and **14** was established by X-ray crystallographic analysis.[43]

Regardless of the electronic character or the position of the substituent, substitution of the phenyl ring had little impact on the reaction outcome with other aryl-substituted ynamides. Thus, **15** and **17** with *para*- or *meta*- methoxy-substituted rings, or **16** and **19** with *para* chloro- or *ortho, ortho* dichloro-substituted rings were all obtained in similar high yields and as single *E* isomers. Only **18** having an *ortho* methoxy-substituted phenyl ring was an exception to this trend as it was delivered with low stereoselectivity. Certainly, coordination of Et_2Zn to the MeO group influences the alkylzinc group transfer event that is the stereodiscriminating step (*vide infra*).

The germylzincation was not restricted to ynamides substituted at the alkyne terminus by aryl groups, as trisubstituted enamides having alkenyl (**20**)-, alkynyl (**21**)-, primary alkyl (**22** and **23**)-, secondary alkyl (**24**)-, and CF_3 (**25**)-substituents β to the nitrogen atom were prepared for the most part in good yields, even if longer reaction times were sometimes necessary. Excellent stereoselectivities were obtained in all cases, but for cyclohexyl- and CF_3-substituted enamides **24** and **25**, reversal of stereoselectivity in favor of a *trans*-selective germylzincation was observed. Furthermore, in the formation of the CF_3-substituted enamide, competitive carbozincation and α-selective germylzincation were detected to some extent. The configurations of products **23** (*E*) and **25** (*Z*) were established by X-ray crystallographic analysis.[43]

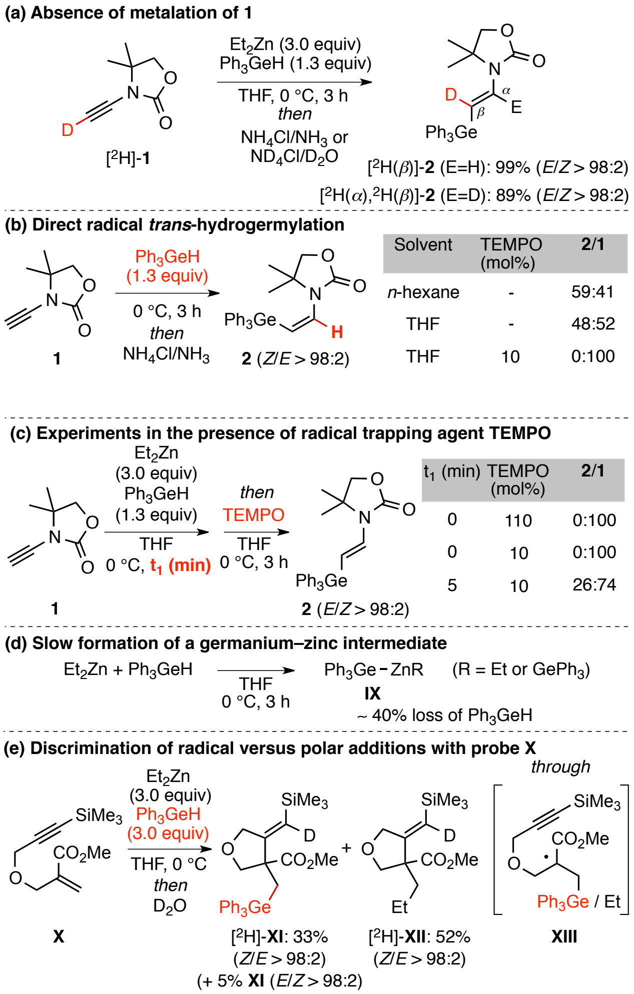
As demonstrated with the preparation of **26** as a single *E* isomer in 88% yield, (2-furyl)$_3$GeH performed as well as Ph_3GeH for the germylzincation of internal ynamides. By contrast, trialkylgermanes were not suitable because of the lack of regiocontrol, as in the case of the formation of **27**.

Finally, similarly to the reactions involving terminal ynamides, D-labeled enamides (> 90% D-incorporation) were obtained on quenching the reactions with ND_4Cl (Scheme 5), thus confirming the formation of vinylzinc intermediates upon reaction of internal ynamides with R_3GeH / Et_2Zn. Again, in the cases of **19** and **24**, quenching with a mixture of CuTC / ND_4Cl / D_2O was necessary to obtain reliable values for D-incorporation.

Our next efforts were directed to gain insight into the mechanism of the new germylzincation reaction. In a first set of experiments, we examined the influence of metalation of **1** in the reaction media (Scheme 6, a). Performing the germylzincation on D-labeled ynamide [^{2}H]-**1** led exclusively to *E*-[^{2}H(β)]-**2** without loss of deuterium at the β-position, thus indicating that deprotonation of **1** (neither by Et_2Zn[44] nor by vinylzinc intermediates) did not occur during germylzincation (in THF at 0 °C).

It was found that Ph_3GeH could react with **1** in the absence of Et_2Zn (Scheme 6, b):[45] both in *n*-hexane and THF, after 3 h at 0 °C, the stereoselective formation of *Z*-**2** was observed in 50–60% yield,[46] and the absence of this direct hydrogermylation in the presence of TEMPO confirmed its radical character.[47] The afore-described D-labeling experiments (Scheme 3) established that germylzincation outcompetes this radical hydrogermylation in THF with excess Et_2Zn. However, the loss of stereoselectivity observed with lower amounts of Et_2Zn or in other solvents (Table 1), can certainly by ascribed to the coexistence of the two competing processes: germylzincation that leads to the *E*-isomer (after work-up), and hydrogermylation that delivers the *Z*-isomer. It is important to note that, by contrast, with internal ynamides, no reaction with Ph_3GeH was detected in the absence of Et_2Zn, even at 40 °C.

Scheme 6. Mechanistic Studies



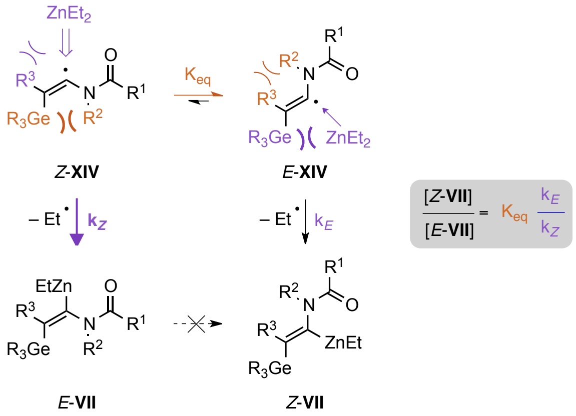
The presence of TEMPO also thwarted completely the germylzincation (Scheme 6, c): no conversion was observed if amounts as low as 10 mol% were added at the beginning and only 26% of *E*-**2** was formed upon addition after 5 min of reaction. While these experiments lend clear evidence for the intervention of radicals in the mechanism, we could not at this point exclude a scenario wherein Et_2Zn would react with R_3GeH by a radical alkylzinc group-transfer process (reminiscent of that involved in the formation of $[(Me_3Si)_3Si]_2Zn$ from $(Me_3Si)_3SiH$ and Et_2Zn)[48] and provide a putative germanium–zinc intermediate **IX** (Scheme 6, d) that would add across the C–C triple bond of the ynamide through a polar mechanism. Notably, the reported formation of $(Ph_3Ge)_2Zn$ by reaction between Et_2Zn and Ph_3GeH in THF required to exclude this possibility.[49] Towards this end, the reaction of Ph_3GeH / Et_2Zn with mechanistic probe **X**[29a] was considered (Scheme 6, e). The formation of cyclized products [^{2}H]-**XI** (33%) and [^{2}H]-**XII** (52%) (arising from competing ethyl radical addition)[50] provided evidence for a radical 1,4-addition (leading to an intermediate β-alkoxy radical **XIII** that undergoes 5-*exo*-dig ring closure) whereas no products arising from the fragmentation of an intermediate β-alkoxy anion[51] (not shown) that would support an alternative polar addition of **IX** were detected. Furthermore, we also monitored by *in situ* ^{1}H NMR the rate of depletion of Ph_3GeH upon contact with Et_2Zn in THF in the absence of ynamide. After 3 h at 0 °C (Scheme 6, d), 40% of the initial amount of Ph_3GeH had disappeared.[52] Hence, the rate of formation of a hypothetical germanium–zinc intermediate under these conditions was too slow to account conveniently for the germylzincation reactions. Overall, these findings provided strong support for the mechanism foreseen at the outset of our work (depicted in Scheme 2) involving the addition of germanium-centered radicals across the C–C triple bond of ynamides.

The regioselectivity of the process was fully consistent with this mechanism, as previous intermolecular additions of radicals across ynamides, including the abovementioned direct hydrogermylation, occured β to the nitrogen atom both for terminal and internal ynamides.[53] Steric effects usually account for the regioselectivity of radical additions across monosubstituted alkynes,[32] and this is likely also the case for terminal ynamides. By contrast, the origin of regioslectivity for internal ynamides is not clear. Steric factors still seem important, as shown by the lack of stereocontrol with the less hindered trialkylgermanes (Scheme 5, product **27**), but other elements, among which stabilization of the vinyl radical by the α-nitrogen atom, or differences in reactivity of the possible regioisomeric radicals in the subsequent forward reaction (S_H2 at zinc), can also intervene and are difficult to estimate.[32]

The stereochemical outcome of the germylzincation reactions was also rationalized conveniently on the basis of this scenario: the stereoselectivity of the germylzincation reaction is that of the alkylzinc group transfer (i.e. **XIV**→**VII**, Scheme 7). sp^2-Hybridized radicals **XIV** have a bent geometry and are considered to exist in two equilibrating diastereomeric forms with a low interconversion energy barrier. The reaction of *E*-**XIV** with Et_2Zn provides *Z*-**VII** and that of *Z*-**XIV** produces *E*-**VII**.[54] Thus, the *Z*/*E* ratio for the formation of **VII** depends both on the relative stability of both isomers of **XIV** (K_{eq}), as well as the relative ease of each diastereomeric form to undergo ethylzinc group transfer (k_Z *vs* k_E). In general terms, one would expect *Z*-**XIV** to react more promptly than *E*-**XIV** ($k_Z > k_E$) because the Et_2Zn/R^3 steric interaction is less demanding that the Et_2Zn/R_3Ge interaction. With "small" R^3 substituents (i.e. R^3 = H, primary alkyl or aryl), the *Z*/*E* equilibrium is largely in favor of the *E* form ($K_{eq} >> 1$) and the formation of

Z-**VII** is favored. By contrast “larger” R^3 substituents (i.e. cyclohexyl or CF_3[55]), destabilize *E*-**XIV** (K_{eq} becomes lower) and thus the formation of *E*-**VII** becomes more favorable.

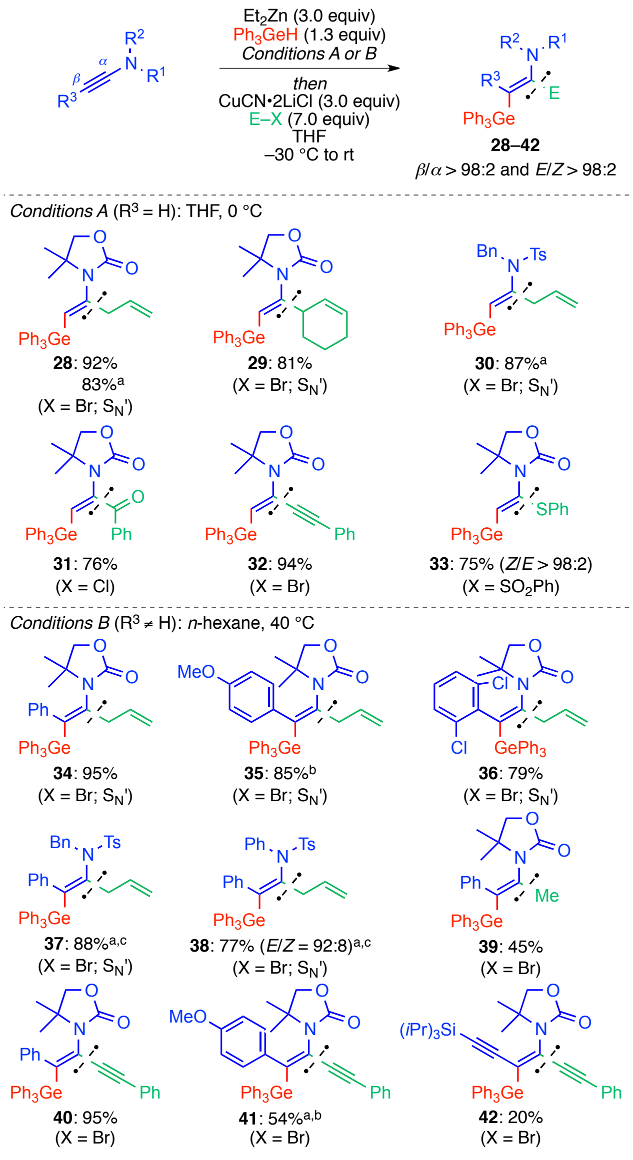
Scheme 7. Stereoselectivity Model for the Germylzincation of Terminal and Internal Ynamides



The reversal of stereoselectivity observed between the radical *trans*-silylzincation of terminal ynamides with $(Me_3Si)_3SiH$ / Et_2Zn in *n*-hexane[29a] and the present *cis*-stereoselective germylzincation in THF is a noteworthy point that deserves further comment. The *trans* selectivity for the silylzincation was attributed to the formation, in *n*-hexane, of a Lewis pair between Et_2Zn and the carbonyl group on the nitrogen atom; the Zn-atom transfer step was accelerated and outcompeted *Z*-to-*E* interconversion of the α-amino vinylic radical that reacted only as the initially formed *Z*-stereomer.[56] As evidenced with *in situ* IR experiments, THF prevents this Lewis-pair formation during germylzincation (*see supporting information)*. Hence, *Z*-to-*E* interconversion becomes faster than the Zn-atom transfer step; the reaction of the *E*-stereomer (i.e. *E*-**XIV** (R^3=H)) is favored and the formation of *Z*-**VII** (R^3=H) is obtained. The fact that silylzincation of terminal ynamide **1** with $(Me_3Si)_3SiH$ / Et_2Zn proceeds with exclusive *cis*-stereoselectivity in THF,[57] provides additional evidence for this remarkable solvent effect.

Having established the scope for the germylzincation reaction, we next investigated the synthetic potential of $C(sp^2)$–Zn bond functionalization to provide access to vinylgermanes with two substituents β to the germanium atom. *In situ* Cu(I)-mediated electrophilic substitution following germylzincation occurred readily with complete stereoretention of the double bond geometry (Scheme 8). The typical procedure involved using the THF-soluble salt CuCN•2LiCl, but (commercially available) CuTC could be used alternatively with comparable results. Both protocols were equally efficient for the vinylzinc intermediates arising from the germylzincation of terminal or internal ynamides, thus giving access to diversely substituted tri- or tetrasubstituted vinylgermanes with defined geometry. Competent carbon and non-carbon electrophiles included allylic halides (**28**–**30** and **34**–**38**), acyl halides (**31**), alkynyl bromides (**32**, **40**–**42**), methyl iodide (**39**) or phenyl phenylthio sulfone (**33**). The *E* configuration of product **40** was established by X-ray crystallographic analysis.[43]

Scheme 8. Domino Ynamide Germylzincation / Cu(I)-Mediated Electrophilic Substitution

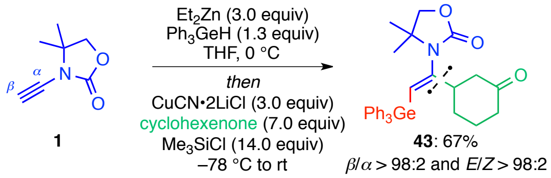


[a] CuTC was used as Cu(I)-salt. [b] Reaction performed at 1.0 mmol scale. [c] The germylzincation was carried out with 2.0 equiv Ph_3GeH at rt.

Importantly, the domino *cis*-germylzincation–Cu(I)-mediated electrophilic substitution was also applicable with tosylynamides (terminal and internal) and delivered α-substituted β-germyl enamides **30**, **37** and **38** in 77–88% yield. It must be noted that the corresponding β-germyl enamides arising from protonolysis (E = H) decomposed during work-up and could not be isolated.

Moreover, *in situ* functionalization of the $C(sp^2)$–Zn bond of the germylzincation adducts was also readily achieved by means of Cu(I)-mediated 1,4-addition to enones, as illustrated with the formation of adduct **43** from **1** (Scheme 9).

Scheme 9. Domino Ynamide Germylzincation / Cu(I)-Mediated 1,4-Addition



The presence of excess Et_2Zn required for the germylzincation step complicated in certain cases clean C(sp^2)–Zn bond functionalization, notably for halodezincation reactions. To overcome this limitation we decided to eliminate Et_2Zn before the electrophilic substitution step by removing the volatiles under reduced pressure. Upon elimination of Et_2Zn, displacement of the Schlenk equilibria (Scheme 4) led to the exclusive formation of divinylzinc intermediates.

In particular, the structure of compounds **44** and **45** was analyzed by X-ray crystallography and both showed similar characteristics (Figure 1). The *cis* geometry between zinc and germanium following germylzincation was confirmed. An almost linear arrangement of the two carbon–zinc bonds was observed, with bond lengths (1.985 to 2.009 Å) in the expected range for diorganozinc compounds.[58] Remarkably, the zinc atom was also coordinated to the oxygen atoms of the carbonyl groups and adopted an uncommon distorted seesaw shaped four-coordinate geometry.[59] The position of the phenyl rings of Ph_3Ge is also of interest. Even though there is no Zn–C_{ipso} contact, two of them clearly shield the Zn atom and likely confer to the divinylzinc species their unusual stability towards hydrolysis and oxidation mentioned previously.

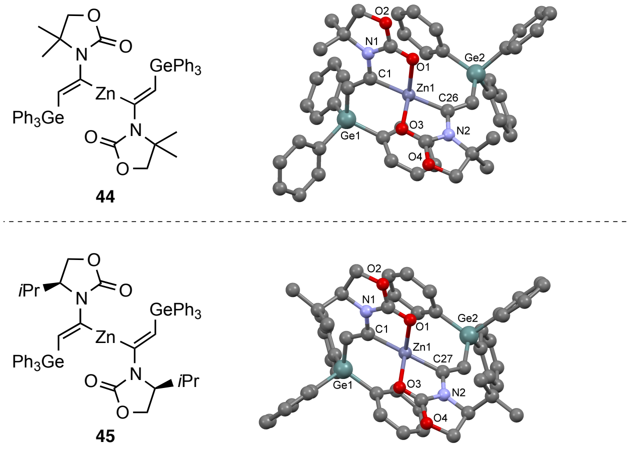
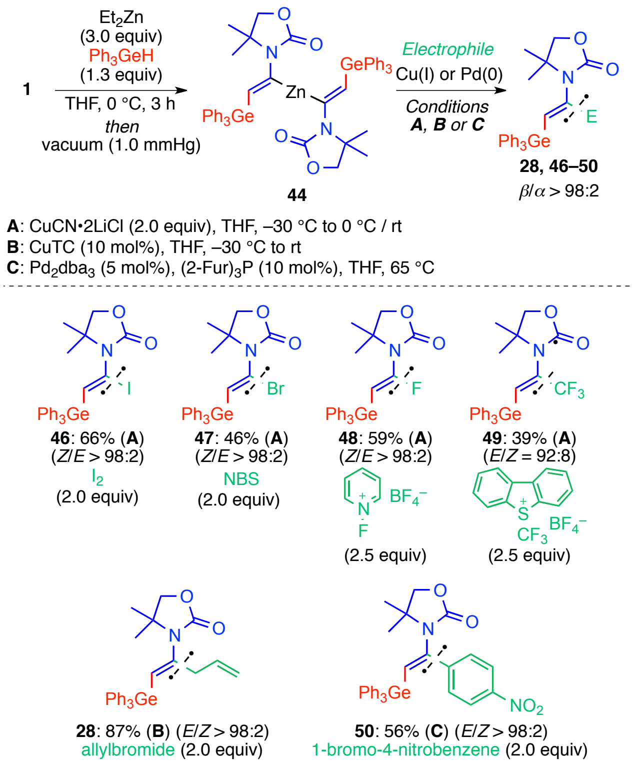


Figure 1. X-ray crystal structure of **44** and **45**. Selected bond lengths and bond angles. **44**: Zn–C1 = 1.995(8) Å, Zn–C26 = 1.985(8) Å, C1–Zn–C26 = 170.8(3)°, O1–Zn1–O3 = 97.8(3)°. **45**: Zn–C1 = 1.989(7) Å, Zn–C27 = 2.009(7) Å, C1–Zn–C27 = 165.5(3)°, O1–Zn–O3 = 91.3(3)°.

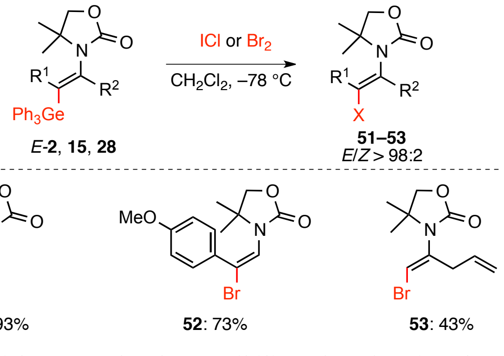
The divinylzinc intermediates arising from the germylzincation / evaporation sequence also underwent smooth Cu(I)-mediated electrophilic substitution in THF and this modified protocol offered additional possibilities for C(sp^2)–Zn functionalization (Scheme 10). The use of halogen electrophiles was possible and β-germylenamides decorated in α-position with iodine (**46**), bromine (**47**) or fluorine (**48**) were prepared in acceptable yields. Trifluoromethylation with Umemoto's reagent to deliver **49** was also accomplished. An additional asset of this protocol was that it made possible the use of catalytic amounts of Cu(I) salt, as shown for the formation of **28** in 87% yield from **1** using 10 mol% CuTC to promote the allylation step. It was also feasible to perform Pd-catalyzed Negishi-type cross-coupling reactions, and **44** reacted with 1-bromo-4-nitrobenzene to afford arylated product **50** in 56% yield. Here, 24% of product *E*-**2** coming from the hydrolysis of unreacted **44** was also recovered. It is noteworthy, that no cross-coupling reaction occurred when 1-iodo-4-nitrobenzene was used under similar conditions.

Scheme 10. Ynamide Germylzincation / Cu(I)- or Pd(0)-Mediated Electrophilic Substitution via Divinylzinc Intermediate 44



To illustrate the synthetic potential of the β-germylenamides accessible through the new germylzincation chemistry, it was then demonstrated that they could be easily converted, with immaculate retention of the double bond geometry, into β-haloenamides that are valuable for further elaboration of stereodefined enamides.[29] Unlike for trialkylvinylgermanes, halodegermylation reactions of triphenylvinylgermanes are sluggish or ineffective.[5b,d,e] Conversely, for β-triphenylgermylenamides, they were remarkably efficient (Scheme 11). Treatment at –78 °C in CH_2Cl_2 of *E*-**2** with ICl resulted in clean halodegermylation providing disubstituted iodoenamide **51** in 93% yield, while reaction of **15** and **28** with Br_2 led to trisubstituted bromoenamides **52** and **53** in 43–73% yields.

Scheme 11. Halodegermylation Reactions of β-Triphenylgermylenamides

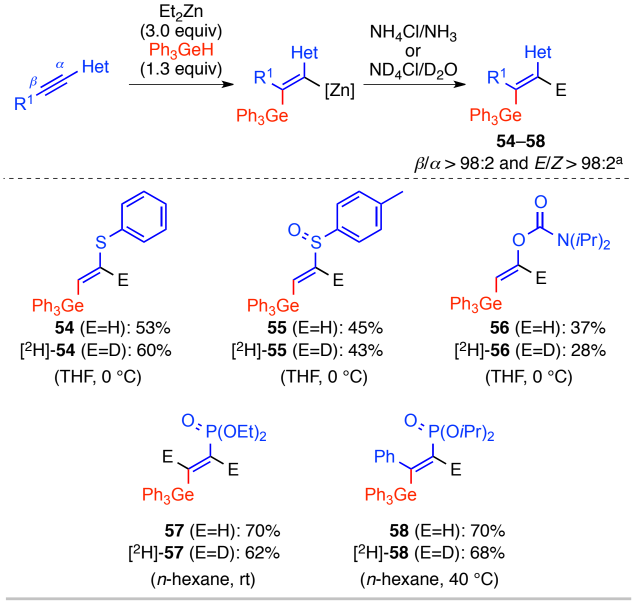


To finish our study, the possibility of performing the germylzincation reaction with alkynes other than ynamides was considered. The addition of Ph_3GeH / Et_2Zn across the carbon–

carbon triple bond of sulfur-, oxygen-, and phosphorous-substituted terminal alkynes occurred at 0 °C yielding the corresponding β-heteroatom-substituted vinylgermanes **54–57** with full β-regio- and *cis*-stereocontrol (Scheme 12). It was interesting to note that the heteroatom substituent had no impact on the regioselectivity, as this trend differed from that observed for certain alkyne carbometalation reactions.[60] THF was generally the solvent of choice, but in the case of **57** better yields were obtained in *n*-hexane. Isolated yields were in the range 37% to 70%. Likewise, tri-substituted vinylgermane **58** was delivered in 70% yield (with the same regio- and stereocontrol) from the germylzincation in *n*-hexane at 40 °C of an internal α-phosphonate-substituted alkyne. The *E* configuration of product **58** was established by X-ray crystallographic analysis.[43]

In all cases, D-labeling confirmed the formation of vinylzinc intermediates and the availability of the C(sp^2)–Zn bond formed for further elaboration, as [^{2}H]-**54**–[^{2}H]-**58** were obtained (> 90% D-incorporation) on quenching with ND_4Cl. In the case of product **57**, D-incorporation α to germanium was also observed indicating that here, germylzincation occurred on the zincated alkyne.

Scheme 12. Germylzincation of Other α-Heteroatom-Substituted Alkynes



54–58

β/α > 98:2 and E/Z > 98:2^a

54 (E=H): 53%
[^{2}H]-**54** (E=D): 60%
(THF, 0 °C)

55 (E=H): 45%
[^{2}H]-**55** (E=D): 43%
(THF, 0 °C)

56 (E=H): 37%
[^{2}H]-**56** (E=D): 28%
(THF, 0 °C)

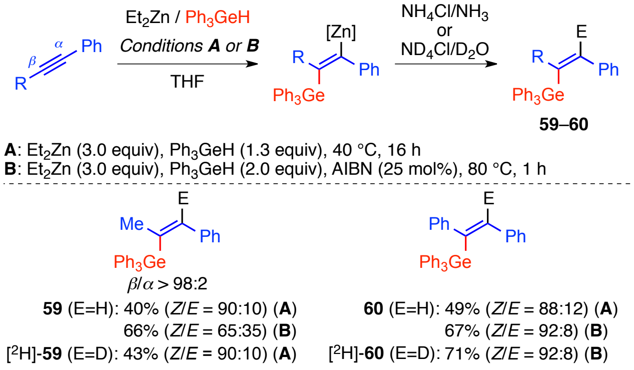
57 (E=H): 70%
[^{2}H]-**57** (E=D): 62%
(*n*-hexane, rt)

58 (E=H): 70%
[^{2}H]-**58** (E=D): 68%
(*n*-hexane, 40 °C)

^{a}Measured by ^{1}H NMR prior to purification.

To finish our study, we next established that the new germylzincation approach was not restricted to α-heteroatom-substituted alkynes and could also be extended to conventional alkynes (Scheme 13). At 40 °C in THF, 1-phenyl-1-propyne and diphenylacetylene yielded products **59** and **60** in respectively 40% and 49% yield in high *trans*-stereoselectivity consistent with a radical chain-transfer mechanism with a Zn-atom transfer under kinetic control. Here, the intermediate vinyl radical (sp-hybridized as the result of the conjugation with the adjacent Ph ring) was expected to be linear, and Et_2Zn to approach from the less hindered side opposite to the bulky Ph_3Ge group.[61] At this temperature however, the reactions did not proceed to completion, a behavior that was attributed to the shortening of the radical chains because of a less favorable radical addition step.[62] This effect was eventually corrected by adding AIBN as radical initiator and operating at 80 °C to ensure its decomposition. Products **59** and **60** were obtained in improved 66% and 67% yields within much shorter reaction times (1 h). Control experiments in the absence of AIBN gave less than 10% conversion under the same operating conditions, what underscored the decisive role played by the radical initiator and provided further support for radical character of the germylzincation. The stereoselectivity remained very high in the case of **60**, but dropped for **59** as the consequence of radical induced isomerization of the intermediate zincated vinylgermanes.[63]

Scheme 13. Germylzincation of 1-Phenyl-1-Propyne and Diphenylacetylene



59–60

A: Et_2Zn (3.0 equiv), Ph_3GeH (1.3 equiv), 40 °C, 16 h
B: Et_2Zn (3.0 equiv), Ph_3GeH (2.0 equiv), AIBN (25 mol%), 80 °C, 1 h

β/α > 98:2

59 (E=H): 40% (Z/E = 90:10) (**A**)
66% (Z/E = 65:35) (**B**)
[^{2}H]-**59** (E=D): 43% (Z/E = 90:10) (**A**)

60 (E=H): 49% (Z/E = 88:12) (**A**)
67% (Z/E = 92:8) (**B**)
[^{2}H]-**60** (E=D): 71% (Z/E = 92:8) (**B**)

CONCLUSIONS

In conclusion, we disclosed here the first germylzincation reaction of C–C triple bonds using a combination of a hydrogermane and diethylzinc in a radical chain process. Ready availability of the reagents, operational simplicity and excellent levels of regio- and stereocontrol are important assets of this reaction that can be performed on terminal and internal ynamides as well as on other sulfur-, oxygen-, and phosphorous-substituted alkynes. The decisive feature of this new approach is the possibility of using the C(sp^2)–Zn bond formed as linchpin for the subsequent installation of carbon or heteroatom substituents with complete retention of configuration through *in situ* Cu(I)- or Pd(0)-mediated electrophilic substitution. This offers a convenient and modular route to elaborated di-, tri- and tetrasubstituted vinylgermanes decorated with heteroatom substituents β to germanium that are useful for the preparation of stereodefined alkenes and cannot be prepared using hydrogermylation chemistry or previously reported germylmetalation reactions.

As part of this work, we also were able to isolate and fully characterize, including by X-ray crystallography, the α-amino β-germyl vinylzinc intermediates arising from the germylzincation of ynamides. These divinylzinc complexes showed exceptional stability towards oxidation and hydrolysis, probably as the result of the very uncommon seesaw coordination of zinc.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Additional data and discussion, experimental details, NMR spectra for new compounds, and X-ray crystal structures (PDF)

Crystallographic information files (CIF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Funding Sources

This work was supported by Sorbonne Université, CNRS and the Agence Nationale de la Recherche (SATRAZ Project, grant n° 2011-INTB-1015-01) which we gratefully acknowledge.

ACKNOWLEDGMENT

Omar Khaled and Cédric Przyblski from IPCM are gratefully acknowledged for HRMS analysis. Aurélie Bernard and Claire Trouffard from IPCM are acknowledged for help with NMR analysis.

ABBREVIATIONS

AIBN, azobisisobutyronitrile; CuTC, Copper(I)-thiophene-2-carboxylate; Me-THF, 2-methyltetrahydrofuran; MTBE, methyl *tert*-butyl ether; TEMPO, (2,2,6,6-tétraméthylpipéridin-1-yl)oxy; THF, tetrahydrofuran.

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(42) More acidic hydrolysis conditions (i.e. DCl/D_2O) were avoided because of the probable acid-sensitivity of β-germylenamides.

(43) Crystal structures were deposited at the Cambridge Crystallographic Data Centre with numbers CCDC 1862400 (***E*-12**), 1862401 (***E*-14**), 1862402 (***E*-23**), 1862403 (***Z*-25**), 1862404 (***E*-40**), 1862405 (**44**), 1862406 (**45**) and 1862407 (***E*-58**) and can be obtained free of charge via www.ccdc.cam.ac.uk.

(44) In the absence of Ph_3GeH, metalation of **1** by Et_2Zn (3.0 equiv) was nevertheless observed both in *n*-hexane (35% after 1 h 40 min at 0 °C) and in THF (43% after 3 h at 0 °C).

(45) It is established that radical hydrogermylation of terminal alkynes with Ph_3GeH can occur to variable extents in the absence of added radical initiators, see ref 15, 16e and 17b.

(46) The reaction between **1** and Ph_3GeH (2.0 equiv) in THF at rt for 18 h afforded **2** in 84% isolated yield with *Z*/*E* = 96:4 (see *supporting information*).

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(52) In fact, an immediate 20% loss of Ph_3GeH was observed on reagent mixing, followed by a much slower disappearance of an additional 20% over 3 h (*see supporting information*).

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(54) *In situ* NMR-monitoring experiments of the germylzincation of **1** in THF at 0 °C showed that vinylzinc intermediate **VII** was formed exclusively with *Z* geometry throughout the reaction course (*see supporting information*). On this basis a possible thermodynamically driven *E*-to-*Z* equilibration process was ruled out.

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(56) Note also that coordination of the carbonyl by a Lewis acid should decrease the electronic density of the nitrogen atom of the carbamate group and thus decrease the rate for *Z*-to-*E* interconversion of **XIV**.

(57) The reaction in THF (0 °C, 3 h) of **1** with $(Me_3Si)_3SiH$ (1.3 equiv) in the presence of Et_2Zn (3.0 equiv) afforded in 78% yield the corresponding β-tris(trimethylsilyl)silyl enamide as a *Z*/*E* = 10:90 mixture (*see supporting information*).

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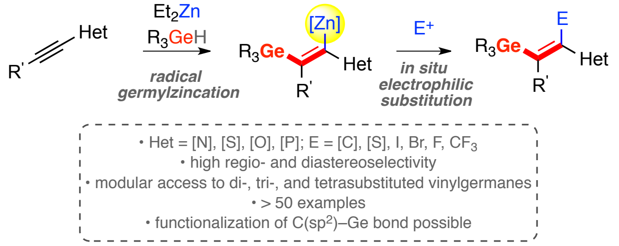
(62) This behavior is counter-intuitive as α-heteroatom-substituted alkynes are regarded as electron-rich and germanium-centered radicals nucleophilic. Nevertheless, since the inductive effect of the heteroatom substituent lowers the energy of the LUMO (see ref 60), a possible explanation is that the addition of the germyl radical benefits from a more favorable SOMO–LUMO interaction for α-heteroatom-substituted alkynes.

(63) The mechanism for the radical isomerization has not been identified but abstraction of allylic hydrogen atoms might intervene with this particular substrate, see: Shimoi, M.; Watanabe, T.; Maeda, K.; Curran, D. P.; Taniguchi, T. Radical Trans-Hydroboration of Alkynes with N-heterocyclic Carbene. *Angew. Chem. Int. Ed.* **2018**, *57*, 9485–9490.



- Het = [N], [S], [O], [P]; E = [C], [S], I, Br, F, CF_3
- high regio- and diastereoselectivity
- modular access to di-, tri-, and tetrasubstituted vinylgermanes
- > 50 examples
- functionalization of $C(sp^2)$–Ge bond possible

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