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Synthesis of 6-membered germacycles by intramolecular germylzincation of alkynes

Seydou Kassamba,^a Mathias Reboli,^a Alejandro Perez-Luna,^b Franck Ferreira^b and Muriel Durandetti^{*a}

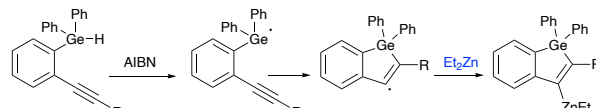
Intramolecular addition of Ge–H bonds across internal alkynes was performed in excellent yields (from 78 to 94% according to the structures) for the first time in one operation with high regio- and stereoselectivities. The key step consists in intramolecular germylzincation of arylgermane cores bearing C–C triple bonds. We first studied the reactivity of dialkylzincs towards Ge–H bonds using hexane as solvent at 80 °C. The *E* configuration of the products suggested that the reaction proceeds following a *syn* addition to the alkyne. Tetrasubstituted vinylgermanes can be obtained in one pot, with retention of the C–C double bond geometry, through Cu-catalyzed electrophilic substitution of the C(sp²)–Zn bond of the vinylzinc intermediates. On the contrary, when the reaction was performed under radical conditions (AIBN), the *Z* isomer were obtained, and no further cross-coupling occurred.

Introduction

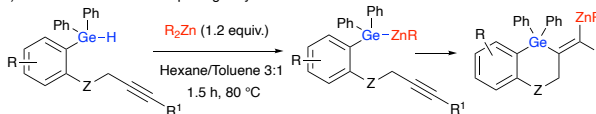
Carbon and its group 14 congeners, silicon and germanium, have structural similarities (valence and geometry), which are at the origin of isostery between them.¹ In recent decades, synthetic chemists have been interested in studying the impact of replacing a carbon atom with a silicon atom not only on the physicochemical properties of target compounds but also on the biological properties of bioactive molecules. These studies have led to important advances in many fields of applications, such as compounds for therapeutic use, perfumes, polymers,² etc. Due to similar physicochemical properties, germanium can also act as a carbon isostere.³ For example, Tacke demonstrated the C–Si–Ge bioisostery⁴ in the case of a peptide containing alanine as α -amino acid, for which the same biological properties were obtained for C-, Si- or Ge-analogues.^{4a} While replacement of carbon with silicon (silicon switch) is more and more frequent, far less works have been focused on analogous germanium switches,⁵ in spite of the fact that organogermanes have been reported to be less toxic than organosilanes.^{5d} Within this context and given that the presence of silicon or germanium atoms increases the lipophilicity of silylated or germylated heterocycles compared to their carbon analogs, our group has engaged in a research program devoted to access original silicon and germanium heterocycles through cyclisation reactions with carbon–element bond formation. We first developed access to silylated and germylated heterocycles based on an anionic rearrangement.⁶ Then, we developed new strategies to access silylated heterocycles through Pd-catalyzed cyclization reactions through C–H activation of a methyl group of TMS,⁷ or Si–Si bond activation⁸ of disilanes. More recently, we disclosed an easy access to germoles by treatment of *ortho*-alkynyl aryl(diphenyl)germanes in the presence of diethylzinc and AIBN as radical initiator (Scheme 1, top).⁹ This approach relies on the combination of germanium radical cyclisation with alkyl zinc group transfer chemistry to achieve intramolecular *trans*-

selective alkyne germylzincation. A key feature of this process is the formation of a C(sp²)–Zn bond that serves as handle for further functionalization in one-pot and thereby paves the way to modular strategies.¹⁰ While alkyne silyl- and germylzincation reactions attract increasing interest,^{11–13} this report represents the first example of intramolecular germylmetallation.⁹

a) Chem. Commun. 2022: Intramolecular radical germylzincation



b) This work: intramolecular polar germylzincation



Scheme 1. Intramolecular germylzincation.

Following this work, we wondered whether germylated heterocycles other than specific germoles could be accessed analogously by intramolecular germylzincation of alkynes involving more challenging cyclisations. Hereafter we report the construction of germacycles by dialkylzinc-promoted 6-*exo-dig* cyclisation of aryl(diphenyl)germanes having *ortho*-positioned pending alkynes (Scheme 1, bottom). The process does not involve a radical cyclisation, but rather the formation of a Ge–Zn reactive intermediate and its intramolecular addition across the C–C triple bond of the alkyne. Thus, this approach will also provide a vinylzinc intermediate for subsequent downstream functionalisation, giving access to new functionalized polycyclic scaffolds useful in diversity-oriented syntheses.

Results and discussion

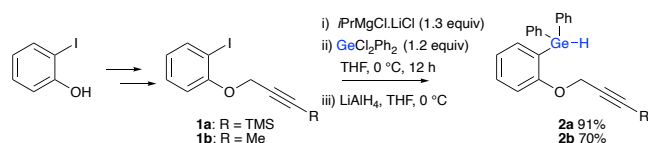
The starting point of our work was the preparation of model arylgermanes **2a** and **2b** having tethered alkynes substituted by a TMS and a methyl group respectively (Scheme 2). Iodoaryls **1** were easily prepared in one or two steps from iodophenol, according to previously reported methodologies.¹⁴ Then, in order to avoid direct carbolithiation,¹⁵ the metalation step was performed using Knochel's turbo Grignard reagent *i*PrMgCl·LiCl,¹⁶ followed by addition of commercially available

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dichlorogermane and subsequent mono-chlorine reduction with LiAlH₄, leading to arylgermanes **2a** and **2b** in 91% and 70% yields respectively.



Scheme 2. Synthesis of arylgermanes **2a–b**.

With compounds **2a–b** in hands, we first considered the conditions developed for the germole synthesis by intramolecular radical germylzincation⁹ (*i.e.* diethylzinc in presence of 0.15 equiv. of AIBN as initiator, in hexane at 100 °C) (Table 1, entries 1–2).

Table 1. Optimization of the reaction conditions for germylzincation of compounds **2a–b**

Entry	2	R ₂ Zn (equiv.)	Solvent	Conditions	3:2 ^a	<i>E/Z</i> Ratio (<i>syn/anti</i>) ^a
1	2a	Et ₂ Zn (3)	Hexane	1h, 100 °C, AIBN ^b	100:0	93:7
2	2b	Et ₂ Zn (3)	Hexane	1h, 100 °C, AIBN ^b	100:0	15:85
3	2a	Et ₂ Zn (3)	Hexane	3h, 100 °C	92:8	81:19
4	2b	Et ₂ Zn (3)	Hexane	3h, 100 °C	71:29	94:6
5	2a	–	Hexane	1h, 100 °C, AIBN ^b	88:12	3:97
6	2b	–	Hexane	1h, 100 °C, AIBN ^b	100:0	0:100
7	2a	–	Hexane	1h, 100 °C	22:78	0:100
8	2b	–	Hexane	1h, 100 °C	70:30	0:100
9	2a	Et ₂ Zn (1)	Hexane/THF 1/2	1h, 100 °C, AIBN ^b	100:0	52:48
10	2b	Et ₂ Zn (1)	Hexane/THF 1/2	1h, 100 °C, AIBN ^b	100:0	22:78
11	2a	Cy ₂ Zn (3)	Hexane/Ether 1/1	2h, 100 °C	100:0	83:17
12	2a	Me ₂ Zn (3)	Hexane/Tol. 3/1 ^c	2h, 100 °C	25:75	6:94
13	2a	<i>i</i> Pr ₂ Zn (3)	Hexane/Tol. 3/1 ^c	2h, 100 °C	100:0	93:7
14	2b	<i>i</i> Pr ₂ Zn (3)	Hexane/Tol. 3/1 ^c	2h, 100 °C	100:0	95:5
15	2a	<i>i</i> Pr ₂ Zn (1.2)	Hexane/Tol. 3/1 ^c	1.5h, 80 °C	100:0	95:5

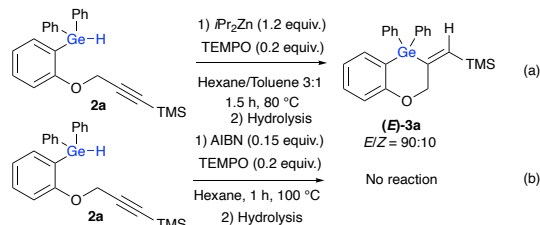
^aDetermined by ¹H NMR analysis of the crude mixture. ^bAIBN 0.15 equiv. ^cMixture of solvents due to the commercial solutions of dialkylzinc reagents.

Full conversion and high regioselectivity in favor of 6-*exo-dig* cyclisation products was observed for both substrates. The stereochemical outcome was however totally different since **3a** was obtained with high *E* selectivity, whereas **3b** was obtained as a *Z/E* mixture, the *Z* isomer being the major one. To our surprise, diethylzinc was found to also promote the cyclisation of **2a–b**, in the absence of radical initiator, with good levels of conversion (70–90%) and stereoselectivity in favor of the *E* isomers regardless of the terminal alkyne substituent (Table 1, entries 3–4). By contrast, reaction without diethylzinc in the presence of 0.15 equiv. of AIBN led to the *Z* isomers with close-to-full stereocontrol and high conversion levels (Table 1, entries 5–6). In the absence of both diethylzinc and AIBN, cyclisation occurred to afford the *Z*-isomer (Table 1, entries 7–8), albeit with incomplete conversion (20–70%). We could then hypothesize that high temperature is the key to Ge–H cleavage. The use of THF as solvent promoted the complete cyclisation to afford the desired products (**3a** and **3b**) as a mixture of stereoisomers (Table 1, entries 9–10), thus indicating a great influence of the solvent. At this stage, we postulated that the cyclisations, leading to **3a–b** could occur through two competitive pathways: a radical hydrogermylation initiated by AIBN or temperature which involves a Ge-centered radical cyclisation and which is *anti*-selective, and a polar germylzincation involving the zincation of hydrogermane⁹ to give a Ge–Zn reagent that undergoes *syn*-addition across the alkyne. According to this scenario, the differences in the *E/Z* ratio between **2a** and **2b** could be explained by a difference in reactivity towards radical cyclisation of the two compounds.

We decided then to test other dialkylzinc reagents to promote the reaction with **2a**, in the absence of AIBN. Changing to dicyclohexylzinc did not improve the selectivity (Table 1, entry 11), while dimethylzinc gave poor conversion and selectivity in favor of the *anti*-addition (Table 1, entry 12). This result is close to that obtained in the absence of dialkylzinc and AIBN (Table 1, entry 7), a sign that in this case dimethylzinc is unreactive and hydrogermylation prevails. DFT calculations have shown that the Me–Zn bond is stronger and less polarizable than for other R₂Zn, which likely prevents the formation of the Ge–Zn bond.¹⁷ Interestingly, 3 equiv. of diisopropylzinc (1.0 M in toluene) gave 93% and 95% yield of **3a** and **3b** respectively with high *E* selectivity, within 2 h at 100 °C, suppressing the radical cyclization path (Table 1, entries 13–14). Moreover, the amount of diisopropylzinc could be reduced to only 1.2 equiv. to afford complete conversion with excellent stereoselectivity in favor of the *syn*-addition products within 1.5 h at 80 °C (Table 1, entry 15). Worthy-to-mention, this allowed us to obtain predominantly either of the *E/Z* isomers, depending on the experimental conditions: 1.2 equiv. of diisopropylzinc at 80 °C in a 3/1 hexane/toluene mixture (conditions **A**, the solvent mixture is due to the commercial solution of diisopropylzinc) lead to the *E* isomer within 1.5 h, while 0.15 equiv. of AIBN as initiator at 100 °C in hexane (conditions **B**) affords the *Z* isomer within 1 h.

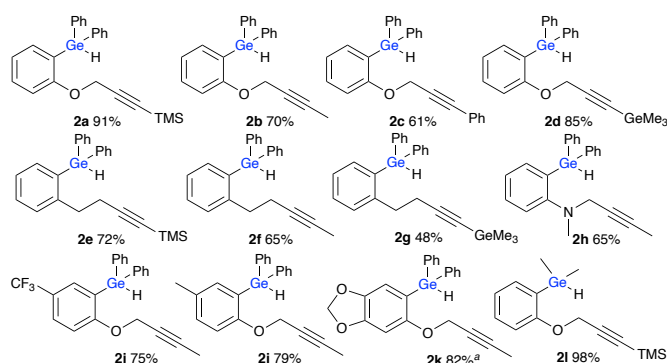
To substantiate the radical or polar nature of the cyclisation reactions, we carried out experiments in the presence of TEMPO, a known radical inhibitor. When the reaction was run under the optimized germylzincation conditions **A** in the

presence of 0.2 equiv. of TEMPO, we obtained complete conversion with the same selectivity in favor of the *syn*-addition product, corroborating that germylzincation does not follow a radical process (Scheme 3a). By contrast, no reaction occurred under hydrogermylation conditions **B** in the presence of both AIBN and 0.2 equiv. of TEMPO (Scheme 3b). These results support the hypothesis of intramolecular germylzincation involving a polar mechanism under conditions **A** and a radical hydrogermylation under conditions **B**.



Scheme 3. Control experiments in the presence of TEMPO.

Focusing on the germylzincation procedure, in order to assess the influence of substituents carried by the C–C triple bond, the aryl moiety and the germanium atom, we prepared several arylgermanes **2a–l** following the procedure depicted in Scheme 2 and involving 2 to 4 steps from commercially available iodophenol, iodoaniline or iodo benzyl bromide (Scheme 4).



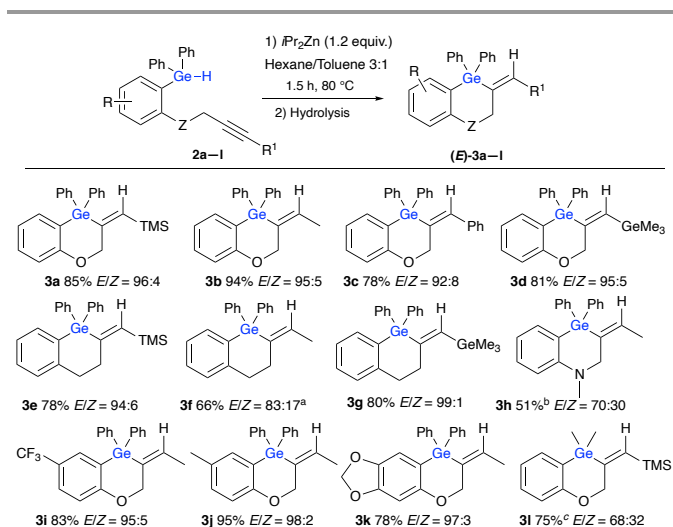
^a The reaction was carried out starting from aryl bromide using 2 equiv. of *t*BuLi

Scheme 4. Synthesis of arylgermanes **2a–l**.

The scope of the germylzincation reaction was next investigated under the previously optimized conditions **A** (Table 2). Results in Table 2 show that the cyclisation takes place in good-to-excellent yields with high stereo- and regioselectivity (*syn*-addition and 6-*exo-dig* cyclisation). The process was efficient with arylgermanes **2a–d**, whatever the substituent on the C–C triple bond, alkyl (**2b**), heteroalkyl (**2a** and **2d**) or aryl substituents (**2c**) being tolerated. The aryl moiety can also bear electron-donating (**2j–k**) as well as electron-withdrawing substituents (**2i**). The reaction was also efficient with **2e–h** analogs, although a decrease in yield and/or selectivity was observed in some cases. In particular, when **2f** was exposed to the germylzincation conditions, we were surprised to obtain 21% of the 7-*endo-dig* cyclized product **3'f** with 66% of **3f**, and in this case with a non-negligible loss of stereoselectivity (*E/Z* =

83:17). As for diphenylgermane **2h**, it led to incomplete 75% conversion, to give 38% yield of compound **3h** (51% BRSM), with a moderate *E/Z* ratio of 70:30. It can be assumed that this alkyne is not sufficiently activated, or that it is misoriented with respect to the Ge–H bond.

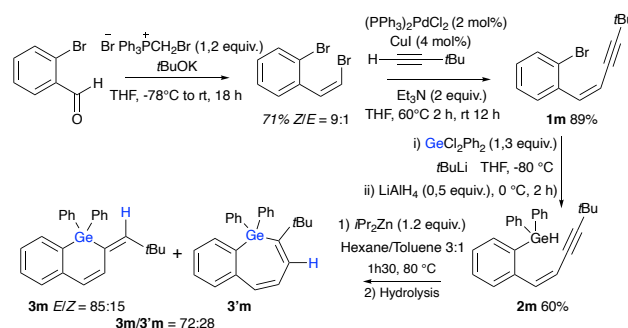
Table 2. Reaction scope for the germylzincation of arylgermanes **2a–l**.



^a21% of the 7-*endo-dig*-cyclic product **3'f** (see Table 4 for structure) was obtained with the 6-*exo-dig* product. ^bIsolated yield based on recovered starting material (75% of conversion). ^cIsolated yield based on recovered starting material (55% of conversion).

Similarly, the optimized procedure did not apply with the same efficiency with dimethylgermane **2l**: the reaction did not exceed 55% conversion, giving 41% yield of compound **3l** (75% BRSM), again with a moderate *E/Z* ratio of 68:32. The poorer results in the last 3 examples may be explained by a less efficient germylzincation process, the loss of stereoselectivity probably resulting from the greater difficulty in activating the Ge–H bond by diisopropylzinc, leaving the competitive hydrogermylation pathway to gain in importance.

We then evaluated the reactivity of enyne **2m**, readily accessible in 3 steps (Scheme 5). Then, germylzincation of enyne **2m** under optimised conditions **A** led mostly to the 6-*exo-dig* product **3m** with a good *E/Z* ratio of 85:15, along with the 7-*endo-dig* cyclisation product **3'm**, as in the case of **2f**.

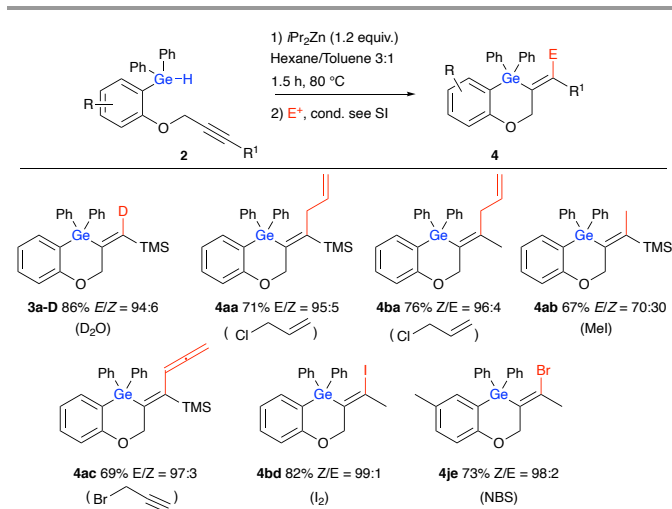


Scheme 5. Synthesis and germylzincation of enyne **2m**.

Note however, that other by-products appear in this case, giving rise to an inseparable mixture by flash chromatography, preventing us to provide isolated yields of **3m** and **3'm**. As mentioned previously, the loss of regio- and stereoselectivity could be due to the enyne C–C triple bond not being sufficiently activated for the germylzincation process to occur efficiently, making hydrogermylation more competitive.

The formation of a vinylzinc intermediate was proved by trapping with various conventional electrophiles.^{9,11–12,18} The formation of a vinylzinc intermediate was first proved by quenching the reaction with D₂O, and compound **3a-D** was obtained in satisfactory 86% yields with full D-incorporation. We were then interested in the allylation of the substrates, in the presence of a copper catalyst (Table 3).

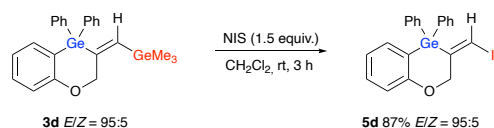
Table 3. Trapping of vinyl zinc intermediates from **2** with various electrophiles.^a



^aIsolated Yields.

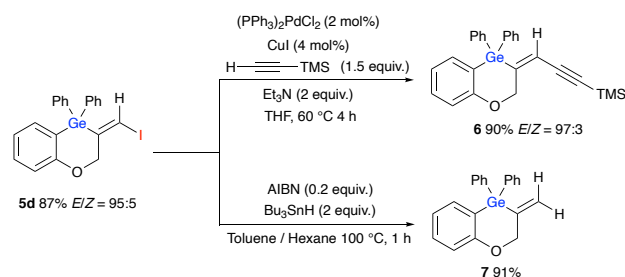
Allylic compounds **4aa** and **4ba** were obtained in good yields (71% and 76 % respectively) with the same stereoselectivity in favor of the *syn*-addition. Reaction with methyl iodide or propargyl bromide afforded compounds **4ab** and **4ac** also in good yields, but with an unexpected loss of stereoselectivity in the case of **4ab**. Finally, vinyl halides were obtained using iodine or *N*-bromosuccinimide as electrophiles, providing **4bd** and **4je** in 82% and 73% yield respectively.

Subsequently, we decided to take advantage of the trimethylgermyl appendage of compound **3d**, by performing an iododegermylation reaction (Scheme 6). Gratifyingly, reaction of **3d** with *N*-iodosuccinimide, using a protocol inspired from Gevorgyan,¹⁹ led stereoselectively to the expected trisubstituted olefin **5d** in fine yield.



Scheme 6. Iododegermylation of **3d**.

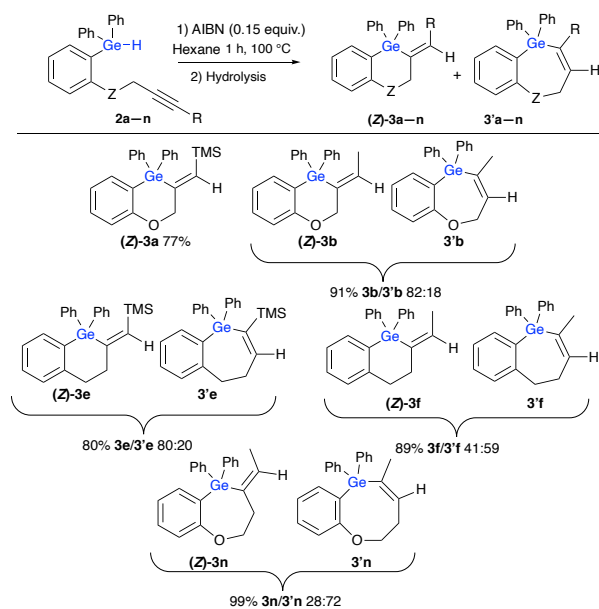
Vinylidide **5d** was finally engaged in a Sonogashira cross-coupling reaction,²⁰ thereby allowing for C–C bond formation from the C(sp²)–Ge bond (Scheme 7). Treatment of **5d** with trimethylsilyl acetylene led stereoselectively to the expected olefin **6** in 90% yield. Also, **5d** could undergo complete dehalogenation,²¹ leading to compound **7** in 91% yield.



Scheme 7. Synthetic applications of **5d**.

During the optimisation step, we found that AIBN alone could initiate efficient intramolecular radical hydrogermylation, leading to *anti*-additions across the C–C triple bond. Also, in some cases, we found a non-negligible loss of regio- and stereoselectivity, which we ascribed to a competitive hydrogermylation process. This process was of interest because even though radical hydrogermylation is a well-known and widely developed process, the vast majority of the reports involve intermolecular additions.²² We thus decided to study the intramolecular hydrogermylation conditions in more detail (conditions **B**), and assess its generality with the substrates shown in Scheme 4 (Table 4).

Table 4. Radical intramolecular hydrogermylation of **2**.^a

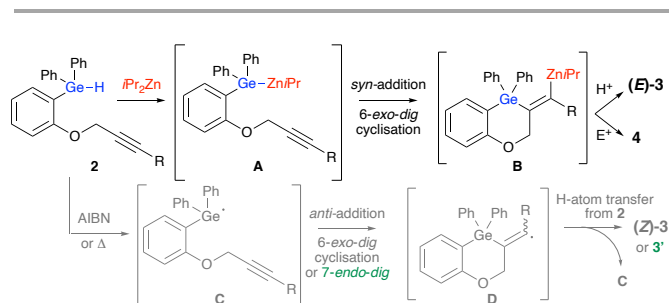


^aIsolated Yields.

Synthetically this was also of interest as conditions **B** (giving *anti*-adducts) and conditions **A** (giving *syn*-adducts) would thus offer complementary stereodivergent procedures. Treatment

of **2a–n** at 100° C with 0.15 equiv. of AIBN, and without dialkylzinc, efficiently triggered intramolecular hydrogermylation within 1 h, but in some cases and depending on the substrate, with a loss of regioselectivity. While **2a** selectively led to the *Z* isomer, by *anti*-6-*exo-dig* cyclisation in about 80% isolated yield, a mixture of **3** and **3'** was obtained from compounds **2b**, **2e**, **2f** and **2n**. The regioselectivity of the cyclisation thus seems to depend on the substituent on the C–C triple bond: *anti*-6-*exo-dig* cyclisation occurs with a highly reactive triple bond carrying a TMS, as in **2a**, while in the other cases, the *endo-dig* process takes place at the same time. These observations are in good agreement with the above-mentioned results for the polar germylzincation of **2f**, for which a loss of regio- and stereoselectivity was noted, and was attributed to a lower reactivity of the C–C triple bond towards dialkylzinc.

Finally, based on all the results, we can propose the mechanistic scenario depicted in scheme 8. In the first step *i*Pr₂Zn reacts with germane **2**, leading to the germylzinc intermediate **A**, which can add to the C–C triple bond by intramolecular (polar) germylzincation, through a *syn*-*exo-dig* cyclisation process, providing vinylzinc intermediate **B**. Subsequently, electrophilic substitution with water or other electrophiles gives the germylated heterocycles (**E**)-**3** or **4**. Alternatively, in the presence of AIBN, or upon thermal activation, radical intermediate **C** is generated. It then undergoes intramolecular addition across the alkyne, providing radical **D** and then (**Z**)-**3** (or **3'** in case of 7-*endo-dig* cyclisation) after H-atom transfer from **2** (which regenerates radical **C** and propagates the radical chain). The *Z*-selectivity of this radical process arises from a preferred H-atom transfer step opposite to the bulky germanium moiety.



Scheme 8. Proposed mechanisms.

Experimental

General Information. All reagents and solvents were purchased from commercial sources and used as received. All manipulations were conducted under argon. The reactions were monitored by thin-layer chromatography (TLC) using silica gel gel (60 F254) plates. Compounds were visualized using a UV lamp (254 nm) and/or by potassium permanganate stain. Flash column chromatography was carried out on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (mp [°C]) were measured with a Kofler apparatus from Wagner and Munz and uncorrected. The infrared spectra of compounds were recorded by transmission on a IRFT spectrometer.

¹H, ¹³C and ¹⁹F NMR spectra were recorded on a spectrometer at 300 MHz (¹³C, 75 MHz). Chemical shifts are given in parts per million. The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet, br.: broad, dd: double doublet, dt: double triplet. High-resolution mass spectrometry analysis (HRMS) were recorded on a Thermo LTQ Orbitrap XL apparatus equipped with an ESI source or on a LCT Premier XE bench top orthogonal acceleration time-of-flight mass spectrometer (Waters Micromass) equipped with an ESI source.

General procedure GP1: Synthesis of arylgermanes (2a–2n). *i*PrMgCl.LiCl (1.3 M in THF, 1.3 equiv.) was added dropwise to a solution of iodoaryls **1**, in anhydrous THF under argon atmosphere at 0°C, and the reaction mixture was stirred for 2 h. Diphenylgermanium dichloride (1.0–1.2 equiv.) was then added and the mixture was stirred at room temperature until completion by TLC (for 10–16 h). The resulting mixture was then cooled to 0°C and LiAlH₄ (0.5 equiv.) was added and the solution stirred at 0°C for 1 h and at room temperature for additional 2 h. The solution was quenched with water and the aqueous layer was extracted with Et₂O (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

General procedure GP2: Polar intramolecular germylzincation ((E)-3a–l, Table 2). In a dry sealed tube under argon atmosphere, germane **2** (0.25–2 mmol) was dissolved in dry hexane and the solution was degassed. *i*Pr₂Zn (1.0 M in toluene, 1.2 equiv.) was then added at room temperature, and the reaction mixture was heated at 80° C for 1.5 h. After cooling to room temperature, the reaction mixture was hydrolyzed with aqueous NH₄Cl and stirred for 20 min. The layers were separated and the aqueous layer was extracted with ether (x3). The combined organic layers were washed with brine (x2), dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

General procedure GP3: Domino polar germylzincation / Cu(I)-mediated electrophilic trapping (4, Table 3). The general procedure GP2 was followed. Instead of hydrolysis, the appropriate Cu(I)-salt (0.2 equiv.) and electrophile (3.6 equiv.) were consecutively added and the resulting mixture stirred at room temperature for 2 h or overnight. The mixture was hydrolyzed with aqueous NH₄Cl and stirred for 20 min. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (x3). The combined organic layers washed with brine (x2), dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

General procedure GP4: Radical intramolecular hydrogermylation ((Z)-3a–n and 3'b–n, Table 4). In a dry sealed tube under argon atmosphere, AIBN (0.15 equiv.) was added to a solution of germane **2** (0.25–2 mmol) in dry hexane and the mixture was

stirred 1 h at 100° C. After cooling at room temperature, the reaction mixture was hydrolyzed with aqueous NH₄Cl and stirred for 20 minutes. The layers were separated and the aqueous layer was extracted with ether (x3). The combined organic layers were washed with brine (x2), dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

Conclusions

In summary, we have developed an intramolecular germylzincation, affording a vinylzinc intermediate, which reacts with electrophiles, such as allyl, alkyl or propargyl halides, to generate original substituted 6-membered germacycles as products with high regio- and stereo-selectivity. However, unlike previous germylzincation approaches, this process follows a polar rather than a radical pathway, as experimentally demonstrated. In addition, a stereodivergent radical hydrogermylation procedure has also been developed, providing access to either (*Z*)- or (*E*)-compounds, depending on the experimental conditions.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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