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Regioselective Cyclotrimerization of Terminal Alkynes Using a Digermyne

Tomohiro Sugahara,[a] Jing-Dong Guo,[a] Takahiro Sasamori,[b]* Shigeru Nagase,[c] and Norihiro Tokitoh[a]

Abstract: *The catalytic activation of neutral small molecules followed by the formation of C–C bonds is a highly important method to increase the complexity and/or value of simple starting materials. We discovered that an isolable digermyne, i.e., a compound with a Ge≡Ge triple bond, acts as a precatalyst for the cyclotrimerization of terminal arylacetylenes to afford the corresponding 1,2,4-triarylbenzenes with absolute regioselectivity. Our results demonstrate that bespoke main-group-element compounds can catalytically activate and transform small neutral organic molecules and induce the formation of C–C bonds.*

Academically and industrially, the catalytic activation of neutral organic molecules, followed by the formation of C–C bonds is a highly important method to increase the complexity and/or value of simple starting materials.[1] For example, cyclotrimerization reactions of alkynes that afford aromatic compounds should represent very important C–C bond formation reactions due to the versatility of the resulting aromatic products.[2,3] Traditionally, transition-metal catalysts have been used for this purpose, as some transition-metal complexes based on *e.g.* cobalt efficiently activate alkynes for (i) oxidative additions, (ii) ring-expansions, and (iii) reductive eliminations under concomitant formation of C–C bonds.[3,4] The reaction mechanism underlying the transition-metal-catalyzed cyclotrimerization reactions of alkynes has been well established.[3,5] Several transition-metal-based catalysts have been developed that are highly efficient both with respect to chemical yields and selectivity,[3,6] and these are superior to catalysts based on main-group elements, although such "transition-metal-free" catalytic systems would be highly desirable in order to avoid the use of precious metals.[7] The reason why similar C–C coupling reactions of neutral small organic molecules in the absence of transition-metal catalysts remain largely unknown could be due to difficulties associated with the reductive elimination process of main-group elements due to the strong covalent bonds between main-group elements and carbon atoms. It is therefore hardly surprising that only few cyclotrimerizations of alkynes catalyzed by main-group elements have been accomplished that proceed *via* redox process of the main-group elements.[8] For example, in the Si_2Cl_6-catalyzed cyclotrimerization of alkynes,[8a] $\cdot SiCl_3$ radicals initiate the radical trimerization. But as such radical reactions usually require high temperatures, the regioselectivity is easily compromised. Yet, the creation of main-group-element catalysts for C–C coupling reactions that proceed via redox processes similar to those in transition-metal-based catalysts remain challenging.

Herein, we report a new transition-metal-free catalytic system for the cyclotrimerization of terminal arylalkynes, which includes a Ge-centered redox process. We discovered that a substoichiometric amount of a previously reported isolable digermyne[9,10] promotes the regioselective cyclotrimerization of several terminal arylacetylenes in high yield. Our results thus demonstrate that bespoke main-group-element compounds can catalytically activate small neutral organic molecules and induce the formation of C–C bonds.[11]

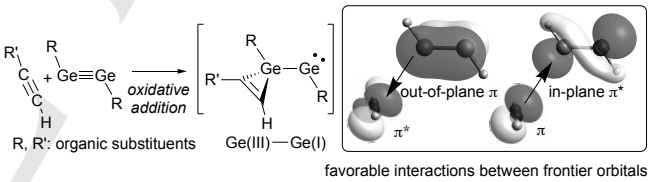

Figure 1. Orbital interactions between digermynes and acetylenes.

Transition-metal complexes readily insert oxidatively into the reactive C–X (X = *e.g.* halogen) or C=C bonds of small molecules, which results in the formation of reactive transition-metal complexes with a higher oxidation state. Subsequently, transmetallation(s) and/or reductive elimination(s) may occur, which enables such transition-metal complexes to act as active catalysts for the transformation of organic compounds. The initial activation process of the small molecules by transition metals, *i.e.*, the oxidative addition, can be interpreted as a simultaneous σ-/π-donation from the small molecule to the transition metal and a π-back-donation from the transition metal to the antibonding orbital of the small molecule.[12] On the basis of a similarly simple concept, the HOMO and LUMO of compounds that contain multiple bonds between group-14 elements such as dimetallynes (E≡E), engage effectively in σ-/π- and π-back-donation with small molecules.[11] The activation of small molecules by such low-coordinated group-14 elements has been intensively investigated, especially with regard to the development of main-group-element catalysts for applications in organic synthesis. However, all reports on the activation of such small molecules by low-coordinated group-14 elements merely accomplish the activation of the small molecules and afford the corresponding adducts as stable compounds due to the formation of strong C–E bonds, which has hitherto prevented a truly catalytic use.[7,11,13] One of the essential

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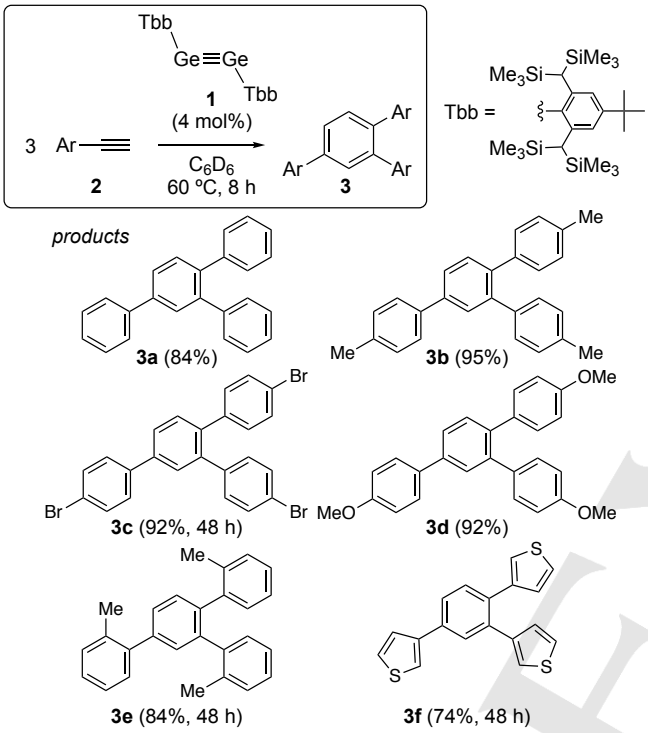
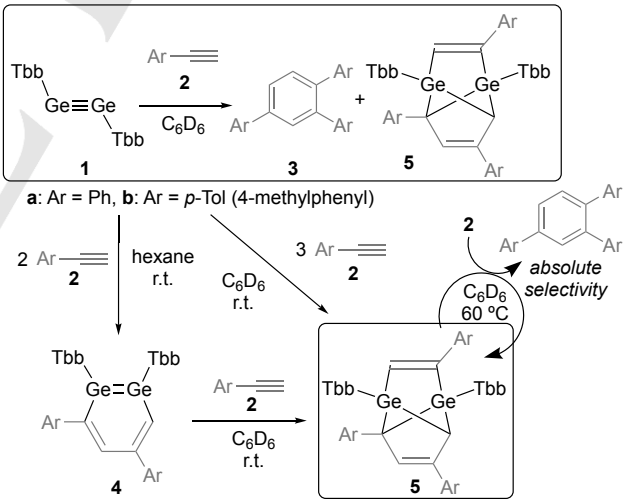
requirements for such prospective main-group-element catalysts is their flexibility with respect to the oxidation state, similar to the case of transition-metal-based catalysts. We have therefore focused our attention on the properties of digermynes (RGe≡GeR, R = organic groups),[11,13,14] as: (i) we have already reported the isolation of stable digermynes and their high reactivity toward compounds that contain C–C multiple bonds, which is due to the low-lying LUMO of the in-plane π*-orbital that results from the *trans*-bent structure;[9,10,13b] (ii) the simultaneous σ-/π-donation and the π-back-donation from/toward the C–C multiple bond agree well with the frontier orbitals of the Ge≡Ge triple bond (Fig. 1);[11] (iii) the possible mixed-valence states such as Ge(III)–Ge(I) should afford sufficient flexibility of the oxidation states. [10,11]



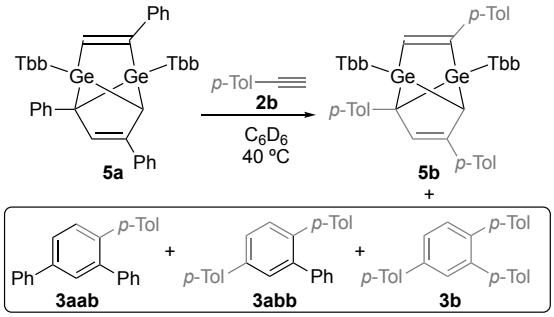
Scheme 1. Regioselective cyclotrimerization of terminal arylacetylenes using a substoichiometric amount (4 mol%) of **1**.

When **1** was treated for 8 h at 60 °C with an excess of PhC≡CH (**2a**) in C_6D_6, the majority of **2a** was converted into 1,2,4-$Ph_3C_6H_3$ (**3a**, 84%). The ^{1}H NMR spectrum of the crude mixture did not show any signals associated with **1**, but new signals arising from **X**, which include the TbbGe- and PhCCH-units. This unexpected result suggested that a small portion of **1** should act as a pre-catalyst for the cyclotrimerization of arylacetylenes. In order to explore the scope of this "Ge-catalyzed cyclotrimerization of arylacetylenes", optimized reaction conditions (4 mol% **1**, 60 °C, C_6D_6) were applied to a variety of arylacetylenes. As shown in Figure 1, phenylacetylenes with *p*-methyl (**2b**), *p*-bromo (**2c**), *p*-methoxy (**2d**), and *o*-methyl (**2e**) substituents, as well as *m*-thienylacetylene (**2f**) exclusively afforded the corresponding 1,2,4-triarylbenzenes (**3b**-**3f**) under these conditions (the formation of **3c**, **3e**, and **3f** required longer reaction times), whereby **1** showed excellent activity as a pre-catalyst (TON = 15~35). Unfortunately, this protocol is not yet applicable to the cyclotrimerization of internal alkynes. Accordingly, these catalytic reactions based on **1** could be termed "Ge-catalyzed Reppe reactions" (Scheme. 1).

Classic Reppe reactions, which use transition-metal catalysts based on *e.g.* Mo or Co to promote the cyclotrimerization of acetylenes, show less selectivity (< ~95%) in some cases, *i.e.*, the purification of these product mixtures is often nontrivial due to contamination with small amounts of *e.g.* the 1,3,5-$Ar_3C_6H_3$ isomer.[3,15] Conversely, in our Ge-based catalytic reactions, by-products such as 1,3,5-$Ar_3C_6H_3$ were not observed, which demonstrates the absolute regioselectivity of these reactions. The products of the Ge-catalyzed reactions presented herein can thus be isolated by simply passing the reaction mixture through a pad of silica gel. Subsequently, we investigated this catalytic reaction in detail to elucidate its reaction mechanism. Treatment of **1** with 2 equiv. of PhC≡CH (**2a**) in hexane at room temperature (r.t.) afforded 1,2-digermabenzene **4a** in 68% yield. The mechanism for the formation of **4a** should be similar to the previously reported reaction of **1** with acetylene that furnishes 1,2-Tbb_2-1,2-digermabenzene.[10] Treating isolated digermabenzene **4a** with a further equivalent of PhC≡CH in C_6D_6 at r.t. afforded **X**, which was unequivocally characterized as 1,6-digermatricyclo[3.3.0.0^{2,6}]octa-3,7-diene (**5a**). Independently, a C_6D_6 solution of **1** was treated with 3 equiv. of **2a** at r.t. to quantitatively generate **5a**. Similarly, **4b** and **5b** were isolated from the reaction between **1** and stoichiometric amounts of *p*-Tol-C≡CH (**2b**) (Scheme. 2). Subsequently, we confirmed that a catalytic amount of isolated **5a** (10 mol%) promotes the quantitative cyclotrimerization of **2a** in C_6D_6 at 60 °C to afford **3a**. These results suggest that **5** should be a key resting state of the active species involved in the catalytic cycle. It can hence be concluded that digermyne **1** works as a pre-catalyst for the cyclotrimerization of terminal arylacetylenes to afford the corresponding 1,2,4-triarylbenzene derivatives, whereby 1,6-digermatricyclo[3.3.0.0^{2,6}]octa-3,7-diene (**5**) represents a resting state for the active catalyst, as another metastable intermediate could not be observed throughout the catalytic reaction.



Scheme 2. Mechanistic studies on the reactions of stable digermene **1** with terminal arylacetylenes.



Scheme 3. Reaction of **5a** with *p*-tolylacetylene (**2b**).

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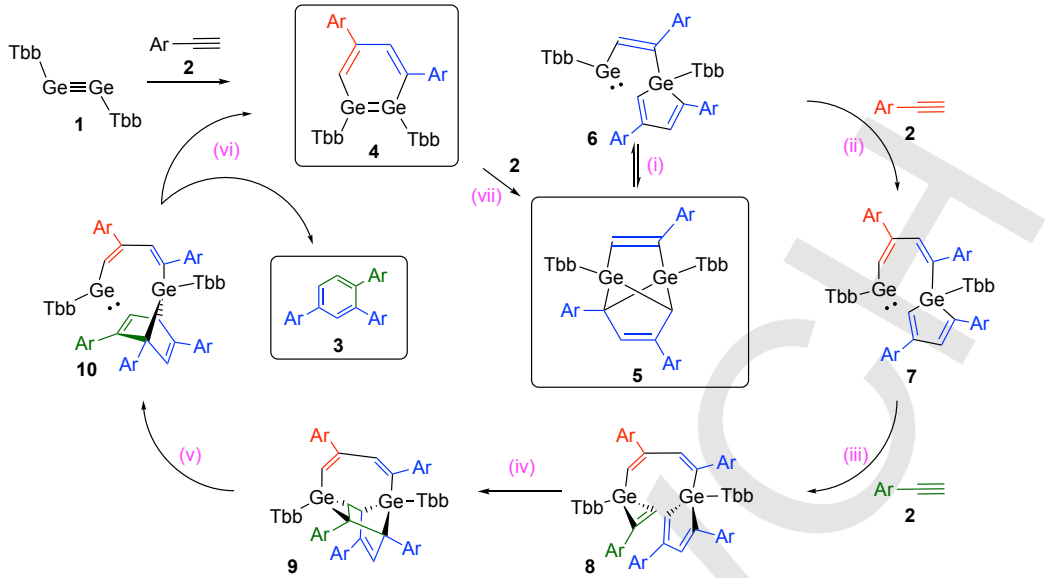

Scheme 4. Reaction mechanism for the cyclotrimerization of terminal arylacetylenes promoted by digermyne **1**.

We monitored crossover reactions between **5a** and *p*-TolC≡CH (**2b**) by ^{1}H NMR spectroscopy (Scheme. 3). Initially, triarylbenzene **3aab** (1-*p*-Tol-2,4-Ph-benzene) was observed as the major product, suggesting that the [Ph_2C_4] moiety of the five-membered [C_4Ge] ring in **5a** reacted with an external alkyne (**2b**) to give **3aab**. Subsequently, the formation of **3abb** was observed under concomitant formation of trace amounts of **3b**, which eventually became the predominant product. Finally, **5a** was completely converted into **5b**.

Considering the entirety of these results in combination with detailed theoretical calculations (TPSSTPSS-D3(BJ)/6-311+G(2d)<Ge,Si>, 6-31G(d,p) <C,H>//opt/3-21G*, Ar = Ph), the reaction should proceed as shown in Scheme 4. We noticed that the reaction barrier from **5** should be the highest among all catalytic reactions, as only **5** is experimentally observed throughout the catalytic cycle. The pathway from **5** most likely involves seven key steps [(i)-(vii)]: (i) an equilibrium between **5** and germole-germylene **6**, (ii) a chain-extension of the germylene moiety in **6** to give germole-germylene **7**, (iii) a [1+2]cycloaddition of the germylene moiety in **7** to give **8**, (iv) an intramolecular [4+2]cycloaddition (Diels-Alder reaction) to furnish **9**, (v) a retro-[1+2]cycloaddition of the three-membered ring (germirane) moiety in **9** to generate germanorbornadiene-germylene **10**, (vi) a retro-[1+4]cycloaddition of the germanorbornadiene moiety in **10** to release 1,2-digermabenzene **4** and 1,2,4-triarylbenzene **3**, and (vii) a regeneration of **5** from **4** and **2**. Each step can be reasonably explained based on the known reactivity of germanium and organic compounds: (i) the structure of **5** can be considered as an intramolecular [1+4]cycloadduct of a germylene and a germole.[16,17] The calculated barriers from **5** to **6** ($\Delta G^{\ddagger}_{5\text{-}6}$ = 21.7 kcal/mol; ΔG = 2.5 kcal/mol) and that from **6** to **5** ($\Delta G^{\ddagger}_{6\text{-}5}$ = 19.2 kcal/mol) suggest that **5** and **6** could be in equilibrium in solution at higher temperature; (ii) the germylene moiety in **6** is reactive toward arylacetylenes. The ≡CH moiety could approach the germylene moiety prior to the C≡C unit inserting into the Ge–C= bond to release thermodynamic energy due to an extension of the π-conjugation (**6**→**7**: ΔG = –10.6 kcal/mol; $\Delta G^{\ddagger}_{6\text{-}7}$ = 14.2 kcal/mol);[18] (iii) germylenes typically engage in [1+2]cycloadditions (**7**→**8**: $\Delta G^{\ddagger}_{7\text{-}8}$ = 4.1 kcal/mol).[19,20] This process should be one of the key steps, as the geometry is determined based on the direction of the approaching arylacetylene due to the steric constraints; (iv) an intramolecular Diels-Alder reaction between the germirene and germole moieties could occur ($\Delta G^{\ddagger}_{8\text{-}9}$ =19.2 kcal/mol). This should be another key step for the stereoselectivity, which can be rationalized using the traditional explanation of Diels-Alder reactions;[21] (v) intermediate **9** exhibits several fused ring systems, including a Ge-containing three-membered ring. The germirane moiety should subsequently undergo a retro-[1+2]cycloaddition to release the strain energy ($\Delta G^{\ddagger}_{9\text{-}10}$ =8.1 kcal/mol);[13b, 19, 22] (vi) the germylene moiety in **10** could promote a facile retro-[1+4]cycloaddition of the germanorbornadiene moiety to furnish the 1,2-digermabenzene together with the elimination of the benzene derivative to gain aromatic stabilization energy.[23] This process is highly exothermic and without barrier; (vii) as the reaction of **4** with **2** generates **5**, we could determine the catalytic pathways: the highest barrier throughout the reactions is the transformation of **5** into **6**.

In conclusion, we have demonstrated that digermyne **1** acts as a pre-catalyst for the formation of C–C bonds in the absence of a transition-metal catalyst, specifically for the perfectly regioselective cyclotrimerization of terminal arylacetylenes. In these reactions, the two Ge atoms undergo mild redox processes between Ge(II) and Ge(IV), which ultimately enables them to transform small organic molecules with a performance that rivals that of transition-metal catalysts. The absolute stereoselectivity of the Ge-catalyst is probably due to kinetically controlled reactions of such main-group-element compounds, while transition-metal-based reactions are usually controlled thermodynamically. Transition-metal catalysts for Reppe reactions promote the cyclotrimerization based on their flexibility to switch between oxidation states, while the combination of Ge(II) (germylene) and Ge(IV) (germole) species stabilizes the redox process during the cyclotrimerization. Low-coordinated main-group-element compounds may thus represent promising prospectives for transition-metal-free catalysts for C–C coupling reactions.

Experimental Section

General Procedure for the catalytic cyclotrimerization of phenylacetylene: In a *J*-Young NMR tube, a solution of digermyne **1** (14.7 mg, 14.1 μmol) in C_6D_6 (0.5 mL) was treated with phenylacetylene (33.4

mg, 0.327 mmol, 23.2 equiv.). After 8 hours, the signals of 1,2,4-tris(phenyl)benzene **3a** (90% NMR yield) were observed in the ^{1}H NMR spectrum. Then, the mixture was filtered through a pad of silica gel (*n*-hexane/CH_2Cl_2 = 10/1) to give **3a** (24.5 mg, 80.0 μmol, 84% yield). Further details are shown in the Supporting Information.

Keywords: Digermyne, 1,2-Digermabenzene, Main-Group-Element Catalyst, Cyclotrimerization, Reaction Mechanism

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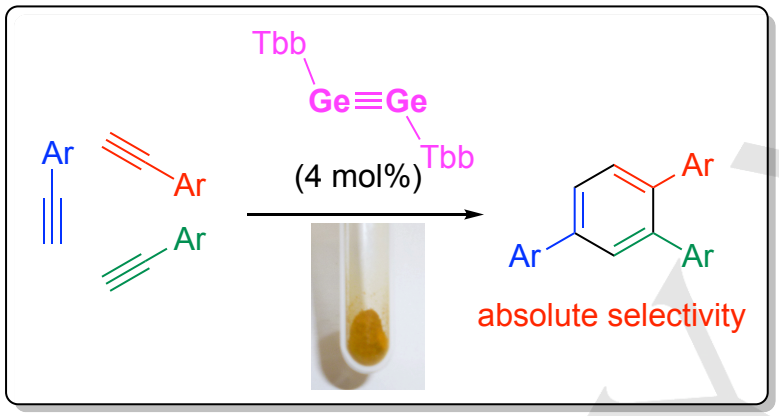
Catalytic Cyclotrimerization by a Main-Group-Element compound



Tbb = 4-*t*-Bu-2,6-[$CH(SiMe_3)_2$]$_2$-C_6H_2

Tomohiro Sugahara, Jing-Dong Guo, Takahiro Sasamori,* Shigeru Nagase, and Norihiro Tokitoh

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