

Letter

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Structure-Modified Germatranes for Pd-Catalyzed Biaryl Synthesis

Hai-Jie Song[‡], Wei-Tao Jiang[‡], Qiao-Lan Zhou, Meng-Yu Xu and Bin Xiao*

Department of Chemistry, University of Science and Technology of China, Hefei 230026, China.

Supporting Information Placeholder

ABSTRACT: Germanium, a member of 14th group, but falls in between Si and Sn, has remained considerably ignored as nucleophiles for a long time. Compared with other forms of Gecontaining nucleophiles, germatranes are structure-defined, easily accessible and stabilized nucleophilic fragments, yet fail to meet the need of high reactivity and facile introducing to organics. Herein, we report a modified structure of germatranes, whose cross-coupling reactivity is greatly improved. The structure can be easily constructed from inexpensive industrial GeO₂, and corresponding *Ge*-Cl and *Ge*-H can also be obtained after facile transformations. Moreover, Ar-*Ge* can be effectively synthesized either from Grignard reagents or Pd-catalyzed germylation of aryl halides. **KEYWORDS:** germatrane, C-C coupling, nucleophiles, palladium, biaryl

In recent decades, Pd-catalyzed cross-coupling reaction has been developed as an effective method that contributes tremendously to biaryl synthesis.¹ Nucleophiles containing boron², silicon³, tin⁴, zinc⁵ or magnesium⁶ had enriched this field remarkably. And for their practicability, corresponding reaction was named after their most leading contributors. More recently, newly explored or developed nucleophiles containing lithium⁷, aluminium⁸, titanium⁹ and may also include aromatic carboxylic acids¹⁰ have expanded the library of cross-coupling, which complement mutually due to their inherent nature, showing extraordinary orthogonalitiy to traditional nucleophiles, which serves as an enlightenment and offers great opportunity and challenge to develop new nucleophiles.

The 14th-group-elements-containing nucleophiles^{3-4,11} usually exhibit many favorable qualities, such as air and moisturestability, shelf-stability and commercializability. Interestingly, germanium(Ge), as a member of 14th group, sits between Si and Sn in the periodic table, draws much less attention^{1,11}. It is presumed that the filling of the fourth period *d* electrons into Ge leads to higher electronegativity¹² than both Si and Sn, which makes Ge-containing nucleophiles suffer from low reactivity. However, some particular properties of Ge¹³ does give it some benefits. For instance, large atomic radius grants it greater coordination ability than Si, and Ge is much more environment-friendly compared with Sn.



Scheme 1. Previous germanium-containing nucleophiles.

Among the developed Ge-containing nucleophiles (Scheme 1), germatranes have obvious superiorities: extra reactivity due to the transannular coordination^{4f,g,14} from nitrogen to Ge, much easier to synthesize than carbagermatranes,¹⁵ it is necessary to point out that the reported synthetic description of carbagermatranes remains ambiguous^{11,16}. What's more, multidentate chelation makes germatranes resistant to hydrolyze, such compounds usually appear as air-stable solids or crystals^{14a}. However, relevant research still remains to be further explored.

Herein, we report a structure-modified germatrane, which derives from inexpensive industrial¹⁷ product GeO₂. Its corresponding *Ge*-H and *Ge*-Cl compound also could be obtained after simple handlings. We proved that such Ar-*Ge* could be extensively synthesized via Pd-catalyzed cross-coupling reaction of *Ge*-H with aryl halides or pseudohalides (Ar-X). Resulting Ar-*Ge* compounds proved to be highly effective for the construction of sp²-sp² carbon-carbon bond. Thus, this research sheds light on the potential of such *Ge*-containing compounds as a cross-coupling partner.



Scheme 2. Optimization of the structure of germatranes.^a

a 0.2 mmol scale, GC yields. See Supporting Information for details.

To acquire suitable structure of germatranes for cross-coupling (Scheme 2), we first synthesized **1a**. To be noticed, various structures of germatranes could be easily synthesized by changing triethanolamine analogs. Thus **1a-1e** were conveniently synthesized through using commercial available PhGeCl₃ and chelating agents which were synthesized from amines and epoxides. To testify the practicability of our reagents, we applied them in a simple system that contained $Pd(Ph_3P)_2Cl_2$ as catalyst. It's found out that the conventional **1a** only give a yield of 55%, which is in accordance with previous research.¹⁶ We assumed that the low reactivity comes from the flexibility of those triethanolamine arms, which makes the dissociation of Ge-O bond prior to the transmetalation of phenyl group. Thus, we decided to add various

gem-dimethyl group onto the cage, hoping to stabilize the transmetalation process by Thorpe-Ingold Effect¹⁸.

To our satisfaction, addition of *gem*-dimethyl group onto the cage does give better yield. Dimethyl (**1b**) and tetramethyl (**1c**) germatrane gave a yield of 65% and 81% respectively (**1a** gave 55%). However, when we applied hexamethyl (**1d**) germatrane in the procedure, yield of the product decreased remarkably. We assumed that such low efficiency comes from the hindered transmetalation, which resulted from significant steric effects. To solve this problem, we changed one arm of the cage into benzo structure (**1e**), leading to an excellent yield of 96%. Further examination of **1f** gave extremely low yield, proving the key to improve the reactivity of the germatranes is the addition of *gem*-methyl group instead of benzo structure.

H₃PO₂

CsCI, HCI

reflux in H₂O

-Cl₂

76%

Ge-OH

III 82%

IV Ge-CI

Et₃N

SOCI2

Ge-H

II 87%

Ge-Cl

IV Quantitative

With optimized structure of germatrane in hand, we next attempted to synthesize this cage structure *from inorganics* (Scheme

Scheme 3. The synthesis of germatrane.

II Ge-H

OH

Table 2. Scope of Pd-catalyzed germatranization.

3), which is of great importance, otherwise we might suffer from the same problem that $ArGeX_3^{19}$ and arylgermanium sesquioxide²⁰ do, which refers to the difficulty to synthesize from aryl halides containing complex functional groups. Luckily we found out that its hydride II can be effectively prepared using I and CsGeCl₃, a compound easily prepared from GeO₂ (See the Supplementary Information for details). What's more, its corresponding hydroxide can be obtained by refluxing I and GeO₂ in water, further work-up with SOCl₂ afforded its chloride IV.

Table 1. Germatranization by Grignard reagents.^a



a 1 mmol scale, isolated yields. See Supporting Information for details.

Similar to the developing history of organoboron reagents, we first tried to prepare Ar-Ge from aryl organometallics. We found out that Grignard reagents reacted with IV smoothly to give products with moderate to good yields (Table 1). Noteworthily, the reaction between phenylmagnesium bromide and the gem-methyl free 1-chlorogermatrane failed to give 1a. The above transformation is the first example of the synthesis of arylgermatranes from organometallics with the cage structure remained. Nevertheless, we focused more on the introduction of Ge to aryl halides. Surprisingly, it turned out that Ge-H is an excellent cross-coupling partner using palladium as catalyst (Table 2). After screening of reaction conditions, the introduction of *Ge* performed effectively for ArI, ArBr, and ArOTf, all afforded good to excellent yields, which is the first example of Pd-catalyzed germatranization reaction. By choosing ligands carefully, Ge-H reacted selectively with I and Br (1p), or Br and Cl (1q), leaving Br or Cl as a further derivatization site. TMS, which was well tolerated in the system, is also a potential coupling fragment (1r). What's more, nitro group was also tolerated (1s), and it's not reduced by Ge-H. Orthosubstituted (1k-n) and even 2,6-disubstituted aryl halides (1m)



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All reactions were conducted on 0.2 mmol scale unless otherwise noted, isolated yields. Conditions: a Pd(Ph₃P)₂Cl₂, Cs₂CO₃, DMAc , RT, 2 h. b Pd(OAc)₂, SPhos, Cs₂CO₃, DMAc, RT, 4 h. c Pd(OAc)₂, DavePhos, Cs₂CO₃, DMAc, RT, 4 h. d 2 mmol scale. e 5 mmol scale. See Supporting Information for details.

gave good yields. Some important fragments in pharmaceutical molecules, such as CF₃ (1w), indole (1x, 1a'), free amide and phenol (1d'-e') as well as various heterocycles can also be well tolerated.

Although the main concern of this study is to generate a series of Ar-Ge reagents, we still examined the scope of the crosscoupling reactions between Ar-Ge and variously substituted aryl bromides (Table 3). Aryl bromides bearing different electronic effects gave perfect yields (3b-i). Both ortho-substituted aryl bromides and ortho-substituted Ar-Ge showed little impact on the yields (3e, 3g-i). By fine tuning, Ar-Ge also performed well with Ar-Cl (3a, 3k-l) and Ar-I (3j), and Br can be well tolerated while using Ar-I as electrophiles. Stille reaction receives a lot of attention due to the fact that it works effectively with heterocycles^{4a}. Thus, we tried some heterocyclic halides in our protocol, and it turned out that thiophene, pyridine, quinoline etc. were also well tolerated (Table 4).

Table 3. Cross-coupling reaction with aryl halides.



All reactions were conducted on 0.2 mmol scale, isolated yields. Conditions: a Pd(Ph₃P)₂Cl₂, TBAF, 2-Me-THF, 80 °C, 12 h. b Pd(Ph₃P)₂Cl₂, TBAF, THF, 80 °C, 12 h. c [(allyl)PdCl]₂, N-(2-methoxyphenyl)-2-(di-tbutylphosphino)pyrrole, TBAF, 2-Me-THF, 85 °C, 12 h. See Supporting Information for details.

Table 4. Substrates scope of biheterocycles.^a



a 0.2 mmol scale, isolated yields. Conditions: Pd(Ph₃P)₂Cl₂, TBAF, 2-Me-THF, 80 °C, 12 h. See Supporting Information for details.

Furthermore, we applied our method in the synthesis of imidazo[1,2-a]pyrimidine derivatives, a group of functionally selective GABA_A ligands that contain typical teraryl substructure, which help to treat or prevent numerous unhealthy symptoms²¹. The synthesis of such derivatives starts from 2b, a common precursor. However, in the beginning of traditional synthesis, less benign SnBu₃ group needs to be introduced after the metalization of **2b** by using $iPrMgBr^{21}$. We managed to realize similar process by applying the standard condition in Table 2, and afforded 1g' effectively. 2c containing Br can be obtained in good yield by using selective cross-coupling reaction condition in Table 3. This provides great convenience in iterative synthesis (Scheme 4a)²² By using this iterative method, $GABA_A$ receptor, such as **3u**, can be synthesized.

Following, we studied the selectivity between Ar-Ge and organoboron during the transmetalation. Cross-coupling took place only between Br and Bpin when two reagents contain Br and Ge, Bpin and BMIDA respectively. Surprisingly, when BMIDA²³ which were primarily exploited by Burke and co-workers and known as fairly stable nucleophilic fragment, reacted with its coupling partner while Ge fragment still remained intact (Scheme 4b).

a Iterative Synthesis via Installing Ge and Selective Cross-Coupling of Aryl Iodide in Presence of Bromides





cat. Pd2(dba)3-SPhos cat. Pd(OAc)2-SPhos K₃PO₄, dioxane/H₂O K₂CO₃, MeCN R 1i' 82% 1j' 72% 1p

Scheme 4. Iterative synthesis and tolerance of Ge group.

Conditions: i. Pd(OAc)₂, SPhos, Cs₂CO₃, DMAc, RT, 4 h; ii. Pd(Ph₃P)₂Cl₂, TBAF, THF or 2-Me-THF, 80 °C, 12 h. See Supporting Information for details.

That TBAF is needed to facilitated the transmetalation of germatranes probably results in the orthogonality of germatranes with Bpin and BMIDA compounds, which reflects the relative inertness of germatranes, however offers us more choices regarding the synthesis of complex products using cross-coupling reactions. Similar to the fact that BMIDA reagents possess an important place in organic synthesis not due to its reactivity but it unique stability, germatranes also stand out for their stability and orthogonality to other reactions.



Scheme 5. Surviving of Ge Group with hypervalent iodide.

Conditions: CuCl, 2,6-bis(tert-butyl)pyridine, DCM, 35 °C, 48 h. See Supporting Information for details.

Applying hypervalent iodide²⁴ compounds in the functionalization of C-H is an important transformation method developed in recent years. We next applied **1a'** in the reported Cu-catalyzed oxidizing arylation reaction condition²⁵. As a result, corresponding product was obtained with a yield of 82% and no Ge-C bond cleavage byproducts can be detected (Scheme 5). However, when 6-indoleboronic acid was employed as starting material, a decreased yield of 55% of **4a** along with 15% yield of deboronation product was detected. This result shows better tolerance of *Ge* than arylboronic acid reagents.

In summary, we developed a highly effective germatrane fragment, which originated from GeO₂. Through simple manipulations, both Ge^+ (e.g. Ge-Cl) and Ge^- (e.g. Ge-H) synthons can be prepared. Also, corresponding metal exchange with Grignard reagents and Pd-catalyzed cross-coupling reactions with aryl halides or pseudohalides can be realized, which is similar to the preparation of organoboron. By our developed methods, various Ar-Ge nucleophilic fragments can be obtained, which exhibit fairly high cross-coupling reactivity. Our study proves that Ge is an element that receives fairly insufficient attention in the periodic table. The effort towards more challenging additive free and/or sp³ crosscoupling of organogermanium reagents is ongoing in our lab.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, Characterization, NMR spectra, and other supplementary data.

AUTHOR INFORMATION

Corresponding Author

binxiao@ustc.edu.cn

Author Contributions

[‡]These authors contributed equally.

Notes

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The authors declare no competing financial interest.

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