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- **Title:** Mechanistic Dichotomy of Magnesium- and Zinc-Based Germanium Nucleophiles in the C(sp3)–Ge Cross-Coupling with Alkyl Electrophiles
- Authors: Weichao Xue, Wenbin Mao, Liangliang Zhang, and Martin Oestreich

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## Mechanistic Dichotomy of Magnesium- and Zinc-Based Germanium Nucleophiles in the C(sp<sup>3</sup>)–Ge Cross-Coupling with Alkyl Electrophiles

Weichao Xue<sup>+</sup>, Wenbin Mao<sup>+</sup>, Liangliang Zhang, and Martin Oestreich\*

**Abstract:** Robust protocols for two mechanistically distinct  $C(sp^3)$ –Ge bond formations from alkyl electrophiles and germanium nucleophiles are reported. The germanium reagents are made available as bench-stable solutions after lithium-to-magnesium and lithium-to-zinc transmetalation, respectively. The germanium Grignard reagent reacts with various 1° and 2° alkyl electrophiles by an ionic nucleophilic displacement. Conversely, the coupling of the corresponding zinc reagent requires a nickel catalyst and engages in a radical bond formation with 1°, 2°, and even 3° alkyl bromides. Both methods avoid the regioselectivity issue of hydrogermylation of alkenes and enable the synthesis of a wide range of functionalized alkyl-substituted germanes.

Low-toxic alkyl- and aryl-substituted germanium compounds possess attractive physical and chemical properties pertinent to material science.<sup>[1,2]</sup> Accordingly, there has been continuous interest in their synthesis, and several methods have been reported.<sup>[3-6]</sup> Of these, (transfer) hydrogermylation of alkenes is a reliable option but usually limited to  $\alpha$ -olefins to arrive at germanes substituted with linear alkyl chains;<sup>[3,4]</sup> electronically unbiased, internal alkenes usually lead to mixtures of regioisomeric α-branched alkyl-substituted germanes. Another common approach is by nucleophilic substitution of alkyl halides and tosylates with lithium-based germanium nucleophiles (Scheme 1, top).<sup>[5]</sup> The high reactivity of these hard germanium reagents is responsible for the poor functional-group tolerance and accounts for undesired side reactions. The reverse approach, that is nucleophilic displacement at chlorogermanes with alkyl metals, is burdened with the same imcompatibility with functional groups and is even less general (Scheme 1, top).<sup>[6]</sup>

Our laboratory recently introduced a procedure for the preparation of bench-stable stock solutions of silicon Grignard reagents, and applied these silicon nucleophiles in iron- and cobaltcatalyzed  $C(sp^3)$ –Si cross-coupling reactions with alkyl bromides.<sup>[7]</sup> A complementary nickel catalysis using zinc-based silicon nucleophiles was independently disclosed by Fu and co-workers.<sup>[8]</sup> Both catalyst/reagent combinations display excellent functional-group tolerance, furnishing functionalized a broad range of alkyl-substituted silanes. Inspired by these reports,<sup>[9]</sup> we considered the formation of soft germanium nucleophiles, e.g., Ph<sub>3</sub>GeMgX (**2**) and Ph<sub>3</sub>GeZnCl (**3**), by transmetalation from lithium in Ph<sub>3</sub>GeLi (**1**)<sup>[10]</sup> to magnesium<sup>[11]</sup> and zinc,<sup>[12]</sup> respectively.

[\*] W. Xue,<sup>[\*]</sup> W. Mao,<sup>[\*]</sup> L. Zhang, Prof. Dr. M. Oestreich Institut für Chemie, Technische Universität Berlin Strasse des 17. Juni 115, 10623 Berlin (Germany) E-mail: martin.oestreich@tu-berlin.de Homepage: http://www.organometallics.tu-berlin.de

[<sup>†</sup>] These authors contributed equally to this work.

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Such metalated germanium compounds were either previously not available or existed only as reactive intermediates. We report here their successful preparation and storage, as well as their application in  $C(sp^3)$ –Ge formation (Scheme 1, bottom).

#### known nucleophilic substitution approaches



**Scheme 1.** Known and new approaches to the preparation of alky-substituted germanes. LG = leaving group. M = Li and Mg. X = Cl and Br.

We began our investigations with the reaction of Ph<sub>3</sub>GeMgX (2) and alkyl electrophiles. To our surprise, we found that germylation occurred without the assistance of a catalyst (see the Supporting Information for details). This stands in stark contrast to related transformations with silicon Grignard reagents.<sup>[7]</sup> Typical leaving groups such as chloride, bromide, iodide, and tosylate were tested (Scheme 2). The latter three cyclopentane derivatives **5a–7a** reacted in good yields whereas cyclopentylchloride (**4a**) only afforded trace amounts of **8a**;  $\beta$ -elimination observed was not seen. This chemoselectivity indicates that Ph<sub>3</sub>GeMgX (**2**) is less nucleophilic than Ph<sub>3</sub>GeLi (**1**).<sup>[5a,5b]</sup>



Scheme 2. Nucleophilic substitution with magnesium-based germanium nucleophile. [a] Estimated by GLC analysis with tetracosane as an internal standard. [b] 2 h for LG = I.

We then explored the substrate scope with Ph<sub>3</sub>GeMgX **2** (Scheme 3). Yields were generally high for primary alkyl bromides containing ether (as in **5b** and **5c**) and acetal (as in **5d**) groups. Acylic (**5e** and **6f**) and cyclic (**5g**) electrophiles underwent the germylation equally well. To our delight, benzylic chloride **4h** and bromide **5h** reacted cleanly to produce desired **8h**. There are however limitations of this straightforward approach: Low yields were observed for tertiary halides **5i** and **6i**, and carbonyl groups were not tolerated (not shown). To distinguish between an ionic and radical mechanism, (bromomethyl)-cyclopropane (**5j**) was subjected to the standard setup; no ring

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opening occurred, and 8j was isolated in high yield (gray box). This outcome likely excludes the involvement of radical intermediates



Scheme 3. Ionic C(sp<sup>3</sup>)-Ge formation of alkyl halides with Ph<sub>3</sub>GeMgX 2. [a] Estimated by GLC analysis with tetracosane as an internal standard. TBS = tert-butyl dimethyl silyl. [b] 2 h for LG = I.

The moderate functional-group tolerance of the ionic  $C(sp^3)$ -Ge bond formation with magnesium reagent 2 was hardly any improvement over the existing methods.<sup>[5,6]</sup> We therefore continued to explore the reactivity of the corresponding zinc reagent 3 in the reaction with alkyl electrophiles (Table 1). After a series of orientation experiments, we found that excellent yield was obtained with NiBr<sub>2</sub>-glyme as catalyst in THF/NMP; cyclopentylbromide (5a) afforded germane 8a in 86% isolated yield (entry 1). A blank reaction clearly showed that the nickel salt as catalyst was necessary (entry 2). This result was totally different from that obtained with the germanium Grignard reagent 2. The influence of solvent deserves particular mention. A combination of THF and NMP was crucial to secure high yield (entry 3); the use of other amide-containing co-solvents also promoted the germylation reaction but in diminished yields (entries 4-6). Aside from Ni(acac)<sub>2</sub>, other first-row metal salts were not effective (entries 7-10). Leaving groups other than bromide were examined but it was only iodide 6a that participated in moderate yield; chloride 4a and tosylate 7a reacted sluggishly (entries 11-13).

Table 1. Selected	examples of	f the opti	mization	reactions	[a]

	LG PI 4a-7a	liBr₂·glyme (10 mol%) n₃GeZnCl <b>3</b> (1.5 equiv) THF/NMP 0 °C for 16 h	GePh <sub>3</sub> 8a
Entry	Substrate	Variation	$Yield \ [\%]^{[b]}$
1	<b>5a</b> (LG = Br)	none	92 (86) <sup>[c]</sup>
2	<b>5a</b> (LG = Br)	w/o NiBr₂·glyme	<5
3	<b>5a</b> (LG = Br)	w/o NMP	8
4	<b>5a</b> (LG = Br)	DMF instead of NMP	52
5	<b>5a</b> (LG = Br)	DMA instead of NMP	77

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6	<b>5a</b> (LG = Br)	DMI instead of NMP	85
7	<b>5a</b> (LG = Br)	Ni(acac) <sub>2</sub> instead of NiBr <sub>2</sub> .glyme	85
8	<b>5a</b> (LG = Br)	FeBr <sub>3</sub> instead of NiBr <sub>2</sub> .glyme	<5
9	<b>5a</b> (LG = Br)	$CoCl_2$ instead of NiBr <sub>2</sub> ·glyme	<5
10	<b>5a</b> (LG = Br)	CuSCN instead of NiBr <sub>2</sub> .glyme	<5
11	<b>4a</b> (LG = CI)	none	<5
12	<b>6a</b> (LG = I)	none	52
13	<b>7a</b> (LG = OTs)	none	11

[a] All reactions were performed on a 0.20 mmol scale. [b] Estimated by GLC analysis with tetracosane as an internal standard. [c] Isolated yield after chromatograpy on silica gel. NMP = N-methyl-2-pyrrolidinone. DMF = N,N-dimethylformamide. DMA = N,N-dimethylacetamide. DMI = N,Ndimethylethyleneurea. acac = acetylacetone.

With this nickel-catalyzed C(sp<sup>3</sup>)–Ge cross-coupling protocol in hand, we evaluated its scope (Scheme 4). Both primary and secondary as well as acylic and cyclic coupling partners performed well with superb functional-group tolerance. Aside from rather robust ether (as in 5c) and acetal (as in 5d), a broad array of carboxyl and cyano groups (as in 5k-n and 5r-v) were compatible with this procedure. Likewise, terminal (as in 5o) and internal alkenes (as in 5w) were also tolerated, leading to a synthetically useful allylic germane in the latter case.<sup>[13]</sup> In accordance with the previous observation (Table 1, entry 11), 8q was chemoselectively formed from 5q without cleavage of the C(sp<sup>3</sup>)-CI bond. Activated alkyl bromides where the bromide is adjacent to a  $\pi$ -system, e.g., benzylic bromide **5q**, allylic bromide **5w**, and  $\alpha$ -bromocarboxyl compounds 5t and 5u, were converted into the corresponding germanes in moderate to good yields. There was no diastereocontrol in the germylation of 1-bromo-4-methylcyclohexane (5x with d.r. = 50:50  $\rightarrow$  8x with d.r. = 54:46). Interestingly, exo-8y (d.r. = 89:11) did form predominantly starting from exo-2-bromonorbornane (5y, d.r. > 99:1).

The method was also applicable to the tertiary alkyl bromides (Scheme 5). Acylic substrates 5i and 5z underwent the germylation in good yields. However, 8i and 8z did form along with other regioisomers such as 9i and 9z, respectively (see the Supporting information for details). Cyclic 5a' and tricyclic 5b') were also probed but yields were ruined by competing β-elimination and/or dehalogenation.

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**Scheme 4.** Nickel-catalyzed  $C(sp^3)$ –Ge formation of alkyl bromides with Ph<sub>3</sub>GeZnCl (3). [a] Yield is for the mixture of isomers, and rs means the ration of tertiary product/other isomers. [b] Estimated by GLC analysis with tetracosane as internal standard. Cbz = benzyloxycarbonyl.

To gain mechanistic insight into this nickel-catalyzed germylation, we conducted a radical-probe experiment again using (bromomethyl)cyclopropane (**5***j*; Scheme 5, top). Indeed, ringopening to the alkene regioisomers **10***j* and **11***j* occurred, and the cyclopropylmethyl-substituted germane **8***j* was found in lesser quantity (cf. Scheme 2, gray box). Also, enantioenriched (*S*)-**5***s* underwent the C(sp<sup>3</sup>)–Ge coupling with complete loss of the stereochemical information to result in *rac*-**8***s* (Scheme 5, bottom). These experiments strongly support the involvement of alkyl radical intermediates which are likely generated by singleelectron transfer from an assumed Ni(I)–Ge species to the C(sp<sup>3</sup>)–Br bond.<sup>[14]</sup> In agreement with the vast majority of nickelcatalyzed Negishi coupling reactions of alkyl halides,<sup>[15]</sup> a plausible Ni(I)/Ni(III) catalytic cycle based on radical pathway is depicted in the Supporting Information.



Having identified the radical nature of this nickel catalysis, we set out to survey the relative reactivity of the alkyl bromides.<sup>[16]</sup> As can be seen from Table 2, the order of reactivity is tertiary > secondary > primary. We interpret this as the stability of the alkyl radical being the dominant parameter in these  $C(sp^3)$ –Ge couplings. However, rearrangement from the more bulky tertiary to less bulky radicals as seen for **5i** and **5z** also demonstrates that the steric effect must be considered in these germylation reactions (cf. Scheme 4, bottom).

Table 2. Competition experiments.<sup>[a]</sup>

R <sup>1</sup> –Br 1.0 equiv	+ R <sup>2</sup> –Br <u> </u>	NiBr <sub>2</sub> ·glym Ph <sub>3</sub> GeZnCl THF 0 °C f	ie (10 mol%)   3 (0.3 equiv) /NMP for 16 h	· R <sup>1_</sup> GePh <sub>3</sub> + F	₹ <sup>2</sup> –GePh₃
	Me 5c'	Br	Me Br Me 5e	Me Br Me Me 5i	
Entry	R <sup>1</sup> –Br	R <sup>2</sup> –Br	Ratio F	R <sup>1</sup> –GePh₃:R <sup>2</sup> –Ge	Ph3 <sup>[b]</sup>
1	5c'	5e	33:67		
2	5e	5i	32:68		
3	5c'	5i	30:70		

[a] All reactions were performed on a 0.20 mmol scale. [b] Estimated by GLC analysis.

Herein, we have described two practical methods for  $C(sp^3)$ – Ge bond formation with readily available, easy-to-handle solutions of magnesium- and zinc-based germanium nucleophiles **2** and **3**. To the best of our knowledge, it is the first time that germanium nucleophiles other than Ph<sub>3</sub>GeLi (**1**) have been used in synthetic chemistry.The reaction of the germanium Grignard reagent with alkyl electrophiles proceeds through an ionic mechanism, i.e., nucleophilic substitution, while the nickel-catalyzed cross-coupling using germanium zinc reagent follows a radical pathway. Broad substrate scope and good yields are particularly seen with the soft zinc reagents, and we therefore anticipate that this method could find widespread use in the preparation of functionalized organogermanium compounds.

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#### Suggestion for the Entry for the Table of Contents

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**Chinese–Germane collaboration.** Homogeneous stock solutions of magnesiumand zinc-based germanium nucleophiles are readily accessible and have been applied to  $C(sp^3)$ –Ge bond formation with alkyl electrophiles. The magnesium reagent reacts directly with alkyl halides and tosylates but the functional-group tolerance is mediocre. Conversely, the cross-coupling of the zinc reagent with alkyl bromides and iodides requires a catalyst and is tolerant towards a broad range of functional groups. W. Xue, W. Mao, L. Zhang, M. Oestreich\*



Mechanistic Dichotomy of Magnesium- and Zinc-Based Germanium Nucleophiles in the C(sp<sup>3</sup>)–Ge Cross-Coupling with Alkyl Electrophiles