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Germylation of Arenes via Pd(I) Dimer Enabled Sulfonium Salt Functionalization

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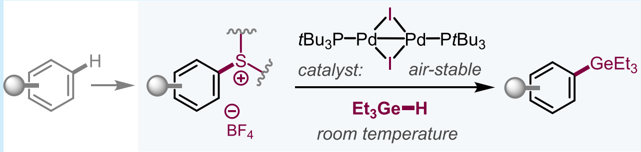

ABSTRACT: While aryl germanes have recently found usage as coupling partners in powerful catalytic applications, the synthetic access to this promising functionality is currently limited. This report details the straightforward synthesis of functionalized aryl triethylgermanes via formal C−H functionalization. Building on the concept of directing-group-free and site-selective C−H functionalization of arenes to thianthrenium salt intermediates, we showcase their efficient couplings with triethylgermane ($Et_3Ge{-}H$) at room temperature, which was enabled by the air- and moisture-stable Pd(I) dimer, $[Pd(\mu\text{-}I)(P^tBu_3)]_2$. The method tolerates numerous functional groups, including valuable (pseudo)halides.

While organosilanes[1] and -stannanes[2] are ubiquitously applied as coupling partners in metal-catalyzed cross-coupling reactions,[3] the corresponding organogermanes have historically found only scarce usage in homogeneous catalysis.[4] This is likely because of early reports that ascribed inferior reactivity to organogermanes as compared to alternative coupling partners.[4] By contrast, very recently, our group developed coupling methods based on Pd-nanoparticle and $\text{Au}^{(\text{I})}/\text{Au}^{(\text{III})}$ catalysis, which enabled the selective and orthogonal functionalization of the organogermane in the presence of silanes, boronic acids, or boronic ester groups as well as a range of additional functionalities (see Figure 1).[5] In this context, the next frontier of applications of the robust and nontoxic organogermanes in synthesis and catalysis will greatly benefit from new and efficient strategies to install the R_3Ge functionality.

The current methodological repertoire largely relies on prefunctionalized arenes, employing aryl (pseudo)halides that are either converted to the corresponding ArMgX/Li, followed by reaction with R_3Ge electrophiles[5,6] or coupled directly with hydrogermane or digermane reagents $(R_3Ge)_2$ under Pd catalysis[4c,7] (see Figure 1). While the former method suffers from the reactive nature of such organometallic reagents that may limit functional group tolerance, the latter required relatively high temperature or a significant excess of germane or showed limited scope. There are only few examples of direct C−H germylation under transition-metal catalysis;[8] these methods are characterized by the need for a directing group (to yield predominantly *ortho*-functionalization),[9] harsh conditions (>100 °C), and limited functional group tolerance.

Clearly, a method that does not require prefunctionalized arenes, but instead allows formal installation of the R_3Ge functionality selectively at Ar−H without the need for a directing group or harsh conditions, would be greatly empowering for this field of research.

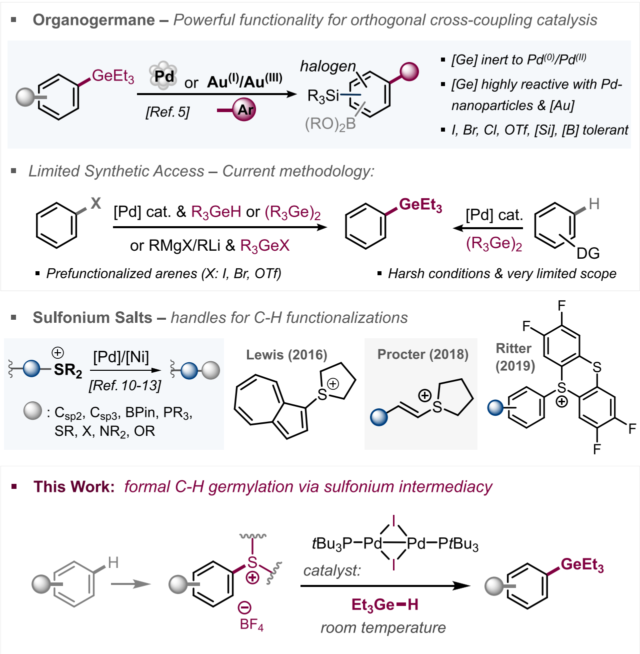

Figure 1. Uses of aryl germanes and their current synthetic access (top) and this work (bottom).

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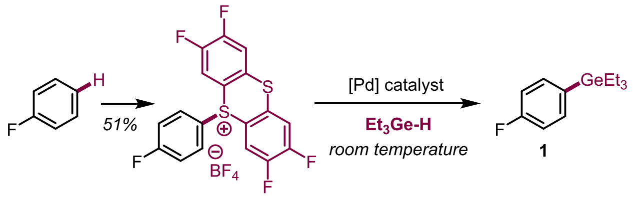
In this context, we were inspired by the recent reports by the groups of Lewis,[10] Procter,[11] and Ritter[12] who demonstrated the elegant concept of first installing a sulfonium salt by formal C−H functionalization of alkenes or aromatics, followed by further C−SR_2^+ derivatizations (see Figure 1). Ritter's thianthrenium approach is especially appealing for its exquisite site-selectivity in aromatic C−H functionalization to C−SR_2^+.[12a] However, while C−C, C−halogen, C−SR, C−BPin, C−N, C−O, and C−PR_3 bond formations via indirectly synthesized[13] or C−H-functionalized C−SR_2^+ salts[10−12] have been showcased,[14] there is no report of the corresponding C_{sp2}−GeR_3 bond formation. With a view toward widening the accessibility of the R_3Ge functionality in organic molecules, we recently set out to investigate the feasibility of a C−H germylation via this concept.

Following the C−H thianthrenation of fluorobenzene with (tetrafluoro)thianthrene *S*-oxide,[12a] we set out to investigate its germylation using triethylgermane (Et_3Ge−H) and different palladium catalysts (see Table 1). We observed that those Pd catalysts that have previously been reported to efficiently transform thianthrenium salts to various functionalities[12a] did not give rise to efficient C−$GeEt_3$ bond formation; either no or only little of the desired aryl germane was obtained, regardless whether $Pd^{(0)}$ or $Pd^{(II)}$ (pre)catalysts were employed (entries 1−5). In contrast, the air-stable Pd(I) dimer [Pd(μ-I)(P^tBu_3)]$_2$, which we previously utilized for a wide range of catalytic transformations,[15] efficiently afforded (4-fluorophenyl)triethylgermane **1** in 82% yield at room temperature in dichloromethane in conjunction with the base DABCO (entry 6).

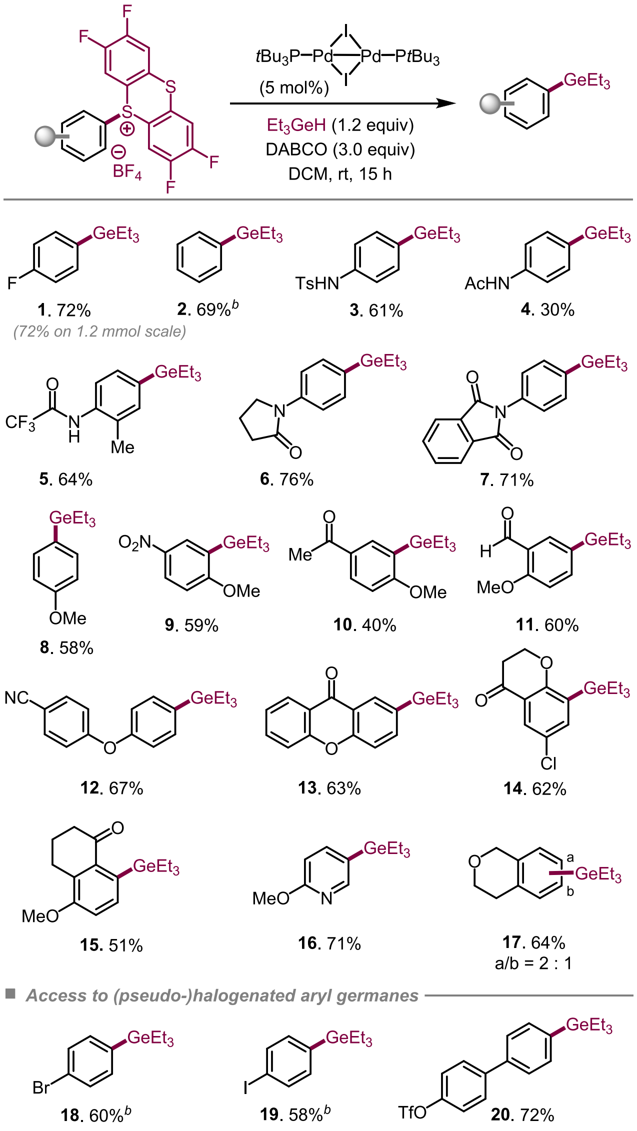
Table 1. Evaluation of Pd Complexes in the Germylation of an Aryl Thianthrenium Salt[a]



entry	[Pd]/ligand	yield of **1**[b] (%)
1	$Pd_2(dba)_3$/Xantphos	22
2[c]	$Pd(OAc)_2/PPh_3$	0
3	$Pd(PPh_3)_2Cl_2$	0
4	Pd(dppf)Cl_2	14
5	$[Pd(P^tBu_3)]_2$	0
6[d]	**$[Pd(\mu\text{-}I)P^tBu_3]_2$**	**82**

[a] Reaction conditions: aryl thianthrenium salt (1.0 equiv), Et_3GeH (1.2 equiv), DABCO (3 equiv), [Pd] cat. (10 mol % Pd), ligand (10 mol %), DCE, rt, 15 h. [b] Yields determined by quantitative ^{19}F NMR analysis of the crude reaction mixture using 1,4-difluorobenzene as internal standard. [c] PPh_3 (17 mol %). [d] DCM was used instead of DCE (75% of **1** was formed in DCE).

Scheme 1. Pd-Catalyzed Germylation of Aryl Tetrafluorothianthrenium Salts[a]



[a] Reaction conditions: aryl tetrafluorothianthrenium salt (0.30 mmol, 1.0 equiv), Et_3GeH (0.36 mmol, 1.2 equiv), DABCO (0.90 mmol, 3.0 equiv), Pd^I dimer (15 μmol, 5 mol %), DCM (3 mL), rt, 15 h. Isolated yields are shown. [b] Yields determined by quantitative ^1H NMR analysis of the crude reaction mixture using mesitylene as internal standard.

With the reaction conditions in hand, we next examined the wider scope of the methodology (Scheme 1). Pleasingly, the protocol proved to be effective for a wide range of compounds, tolerating electron-donating, electron-withdrawing, or no substituents (**2**). Various aniline derivatives reacted smoothly with triethylgermane to afford the corresponding *p*-arylgermanes in moderate to high yields (**3**−**7**). Moreover, several anisole-containing germanes could be synthesized. The method shows a high functional group tolerance since phenoxy, carbonyl, amide, nitro, nitrile, and chloride substituents are tolerated in the germylation. These functionalities are of utmost value for further derivatizations. Additionally, the triethylgermanium moiety can be selectively installed to a wide range of hetero- or polycyclic scaffolds that are present in various natural products and bioactive compounds, such as xanthone (**13**), chromanone (**14**), 1-tetralone (**15**), and pyridine (**16**). However, in the case of the electronically and sterically less distinct isochromane, a mixture of isomers was obtained during thianthrenation, resulting in the same ratio of isomers of the corresponding aryl germanes (**17**). In a few cases, reduction of the aryl tetrafluorothianthrenium salt was observed during germylation, leading to the recovery of initial arene substrate. This competing side process was also reported previously for metal-catalyzed germylation[7b,c] and silylation[7b,16] reactions.

Synthetic access to halogenated aryl germanes would be especially appealing, as these compounds would be ideal platforms for selective and modular derivatizations in the context of cross-coupling catalysis (see Figure 1). We therefore initially evaluated the relative reactivity of (pseudo)halides in germylation as compared to the reactivity of tetrafluorothianthrenium salt. While the aryl iodide afforded the germylated arene in 37% yield under these conditions, the corresponding aryl bromide and triflate gave only traces of the germylated products (≤4%). As such, the selective germylation of a thianthrenium-derived (pseudo)halogenated arene appears feasible. Indeed, when we tested the *intra*molecular competition of C−SR_2^+ versus C−X (X = I, Br, OTf), we succeeded in the selective functionalization of the C−SR_2^+ bond while leaving C−OTf and C−I/Br sites untouched (Scheme 1, bottom). The corresponding (pseudo)halogenated aryl germanes **18**−**20** were obtained in good yields. Potential (di)germylated side products were not detected.

Notably, there is not necessarily a need to purify the aryl tetrafluorothianthrenium salt intermediate by column chromatography; simple isolation by extraction, followed by direct Pd-catalyzed germylation, was also effective. Pyrrolidone derivative (**6**) was successfully prepared in this manner. In addition, the methodology also appears to be suitable for scale up: we conducted a germylation on 1.2 mmol scale, which gave **1** in 72% isolated yield (0.4 g). In this context, it has previously been shown that the thianthrenium moiety can readily be recovered and reused,[12a] which is another benefit over the germylation of prefunctionalized arenes, such as aryl halides.

In conclusion, we have developed a mild and selective Pd-catalyzed germylation via formal C−H functionalization of nonactivated and directing group free arenes facilitated by tetrafluorothianthrenium salts as key intermediates. The transformation allows for the presence of sensitive functional groups, heterocycles, and halides, which provides a rich array of aryl germanium compounds for applications in synthesis and catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01609.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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