ORGANOMETALLICS

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Palladium-Catalyzed Remote *meta*-Selective C−H Bond Silylation and Germanylation

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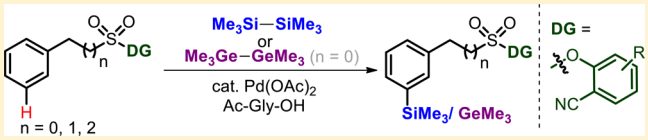
Supporting Information

ABSTRACT: Selective *meta*-C−H activation of arenes to date has met with a limited number of functionalizations. Expanding the horizon of *meta*-C−H functionalization, herein we disclose an unprecedented *meta*-silylation and -germanylation protocol by employing a simple nitrile-based directing template. Longer linkers between the target site and the directing template were successfully explored for *meta*-silylation (sp^2-ε and sp^2-ζ). Additionally, synthetic utility was demonstrated with several postsynthetic elaborations and with a formal synthesis of TAC101, a promising drug for the treatment of lung cancer.



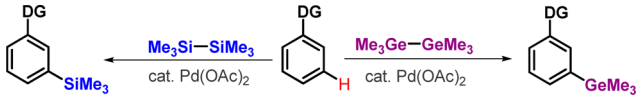
INTRODUCTION

Development of an efficient method for C−Si bond formation has received substantial attention due to the immense significance of silylated entities in synthetic,[1] medicinal,[2] agrochemical,[3] and material chemistry.[4] Organo-silicon compounds are considered as valuable precursors for late-stage modification in organic synthesis, as silicon moieties are easily transformable to versatile organic functionalities through cross-coupling reactions[1a,d,f−h] or *ipso* substitution.[1c,e] In drug discovery, the replacement of a carbon atom by silicon in existing marketed drugs is a vivid research area in the search for new druglike candidates with modified biological properties: i.e., increased lipophilicity and altered efficacy and pharmacokinetic profiles.[5] The high abundance, low cost, and environmentally benign nature of silicon make it suitable for a readily acceptable component for preparing advanced materials and alternating copolymers.[4a]

Conventionally, arylsilanes are prepared either from the reaction of an organometallic intermediate with silicon electrophiles[6] or transition-metal-catalyzed coupling reactions between aryl halide and hydrosilane/disilane.[7] In this context, directed C−H silylation could be advantageous in terms of atom economy, mild reaction conditions, and selectivity.[8] In recent years, *ortho*-directed C−H silylation has been reported in the literature through a five- or six-membered metallacyclic intermediate.[9] However, *meta*-C−H silylation is considered extremely challenging, owing to the large strain energy associated with more than 11-membered metallacyclic intermediates (Scheme 1). The judicial design of directing groups and placement of a suitable linker to connect the directing group and the targeted C−H bond is of paramount importance in addressing this challenge.[10] In other ways, *meta*-C−H activation was also achieved using electronic, steric biasness, or transient directing group strategies.[11]

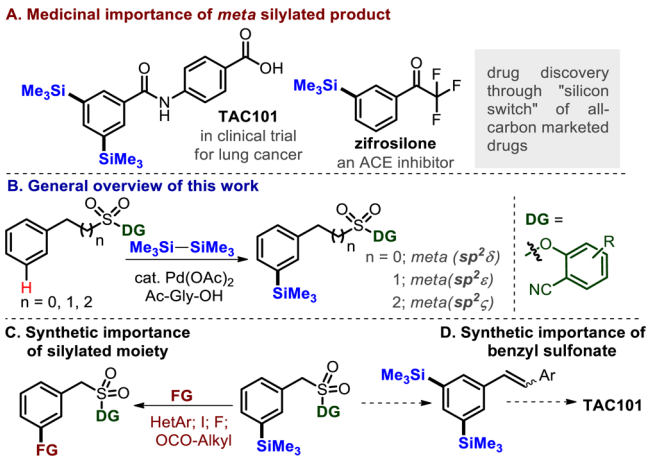
With the pioneering work by Yu group[12a] and recent development of directed *meta*-C−H functionalization[12−15] and

Scheme 1. Directing Group Assisted *meta*-C−H Silylation and Germanylation



intrigued by the importance of silylated entity, we intended to develop directed *meta*-silylation with an easily attachable and removable directing template for benzylsulfonates, since benzylsulfonates are considered as useful synthons for several organic transformations utilizing their α-sulfonyl carbanion (Scheme 2).[13b,e,16] Moreover, a considerable effort was made to silylate 2-phenylethanesulfonic acid and 3-phenylpropane-1-sulfonic acid derivatives by overcoming a consequent rise in

Scheme 2. Importance and General Overview of the Work



Received: April 21, 2017

DOI: 10.1021/acs.organomet.7b00309
Organometallics XXXX, XXX, XXX−XXX

strain energy associated with larger metallacyclic intermediates (12-membered and 13-membered, respectively) (Scheme 2).

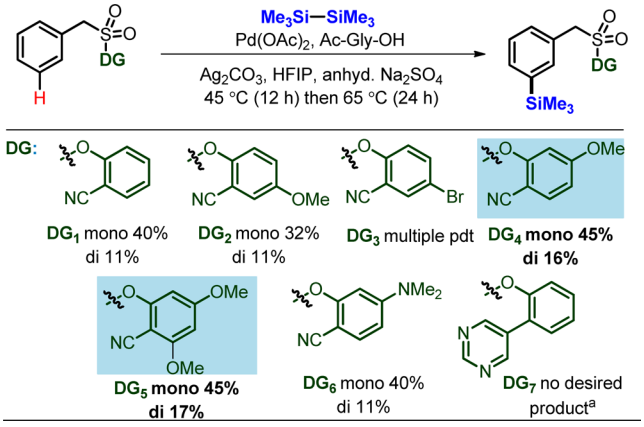
Though organogermaniums have been widely used as valued organic materials,[17] the formation of C−Ge bonds through C−H activation has been rarely studied.[9a] In this report, germanylation of the *meta*-C−H bond of benzylsulfonate has also been developed to address the earlier synthetic shortcomings to access the organogermanium compounds.

RESULTS AND DISCUSSION

During initial exploration, we attempted the silylation of benzylsulfonate with 2-cyanophenol as directing template and hexamethyldisilane as a silylating agent. A combination of $Pd(OAc)_2$, Ac-Gly-OH, and Ag_2CO_3 at 100 °C in hexafluoroisopropyl alcohol (HFIP) as solvent gave only 11% monosilylated product (conversion 13%) with exclusive *meta* selectivity.[18] Such a low conversion is likely due to the deactivation of Pd(II) catalyst to Pd(0) and full reduction of the silver(I) salt to Ag(0) at 100 °C by hexamethyldisilane. To minimize the catalyst waste through this sacrificial reduction, we decreased the reaction temperature and, with a gradient temperature of 45 °C (for first 12 h) and then at 65 °C (for next 24 h) along with portionwise addition of hexamethyldisilane, provided a better yield of the desired *meta*-silylated product. After an extensive optimization of reaction conditions, a total yield of 51% of the *meta*-silylated product (40% mono, 11% di) was achieved.

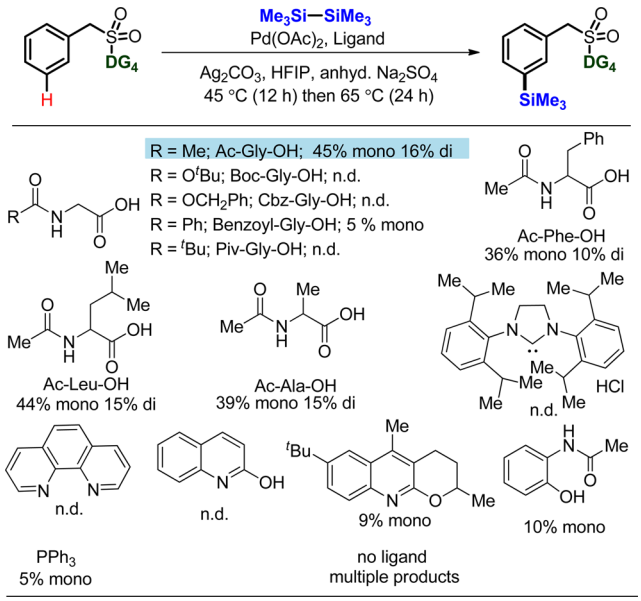
Furthermore, we envisioned that modification of the directing template may play a key role in improving the nitrile coordination for effective *meta*-C−H palladation. Accordingly, by tuning the electronic properties of the 2-hydroxybenzonitrile moiety, it was found that 2-hydroxy-4-methoxybenzonitrile led to the best result with 61% of silylated product (Table 1, 45% mono, 16% di). With 2-hydroxy-4-methoxybenzonitrile as the directing scaffold, further ligand optimization proved that Ac-Gly-OH is an appropriate ligand among others for better reactivity and selectivity (Table 2).

Table 1. Directing Template Optimization[18]



[a]reaction was done at 45 °C; 30 h.

Table 2. Ligand Optimization[a,18]



[a]n.d.: no desired product detected.

Proceeding further with this optimized condition, we explored the *meta* silylation for a broad range of benzylsulfonate ester moieties. Expectedly, the reaction was found to be compatible with fluoro, trifluoromethyl, methyl, chloro, and trimethylsilyl substituents present in the benzene ring (Table 3). Intrigued by the medicinal relevance of fluoro-substituted arenes, we tested this silylation protocol for different monofluoro-, difluoro-, and trifluoro-substituted benzylsulfonates. Interestingly, mono- and difluorinated substrates, with two available *meta*-C−H bonds, provided the corresponding silylated products in 65−76% yield (**2b−e**). As expected, difluoro-substituted substrates with two unsymmetrical *meta* positions yielded both of the monosilylated products in unequal ratios (**2d−e**). 2-Methylbenzylsulfonate afforded only a single mono product due to the possible steric restraint at the other *meta* position by a methyl group (**2f**). Similarly, a 10:1 ratio for *meta*:*meta*′ (**2g**) was observed for the 2-chlorobenzylsulfonate derivative. Furthermore, tolerance of the chloro substituents further demonstrated the versatility of this method, as a chloro group can be utilized for late-stage organic functionalization. As anticipated, both electron-donating and electron-withdrawing substitution at the 3-position of the aromatic ring provided moderate to good yields of the monosilylated products (**2h−l**).

Next, we planned to functionalize the *meta*-C−H of 2-phenylethanesulfonic acid (sp^2-ε) and 3-phenylpropane-1-sulfonic acid (sp^2-ζ) derivatives. The increment of distance between the targeted C−H bond and the metal directing site is expected to cause an elevation in the consequential strain energy and disfavor the entropy factor for the formation of the critical macrocyclic transition state. Encouragingly, the desired silylated products were achieved successfully. Moderate to good yields of silylated product were observed for 2-phenylethanesulfonic acid derivatives with electron-deficient (**3b**,**d**, Table 4) and electron-donating (**3c**) substituents in the aromatic ring (Table 4). In the case of 3-phenylpropane-1-sulfonic acid (**4a**), an excellent *meta* selectivity with useful yield was observed (Table 4).

In order to test the generality of our protocol, we tested other disilane reagents. Unfortunately, under our reaction conditions aryldisilanes failed to generate *meta*-silylated product (Table 5).

In synthetic chemistry, organogermanium compounds have immense applications but there exist limited methods to prepare this class of compounds. In this context, we planned to prepare *meta*-germanylated arenes by developing a protocol

DOI: 10.1021/acs.organomet.7b00309
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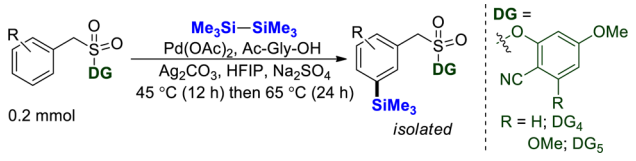
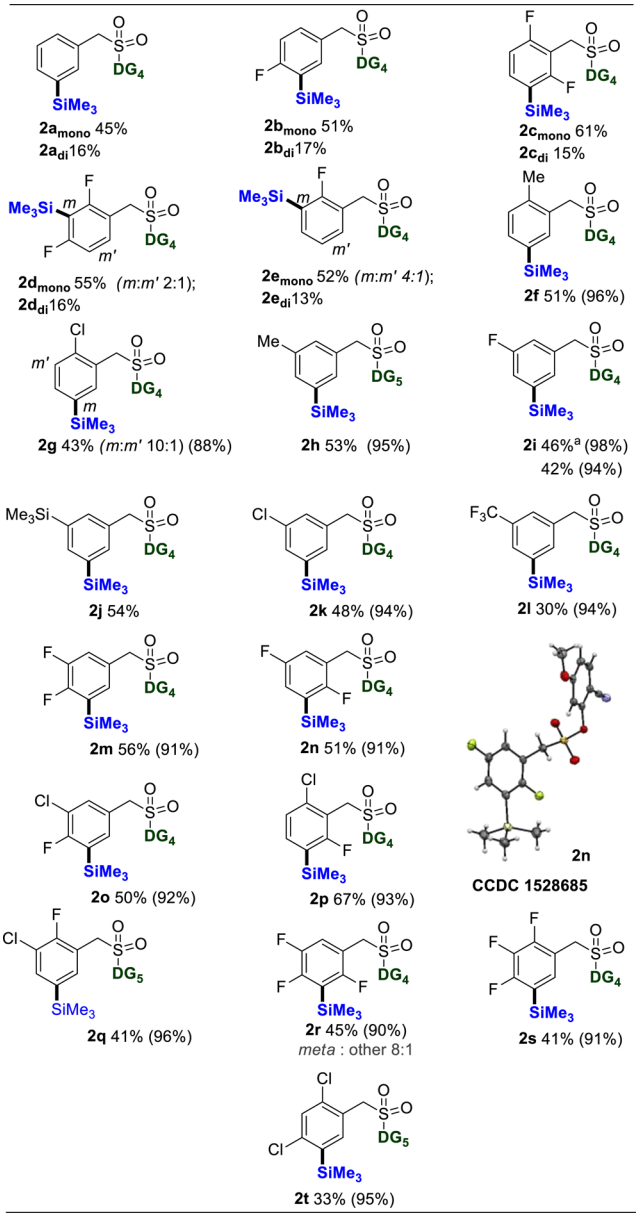
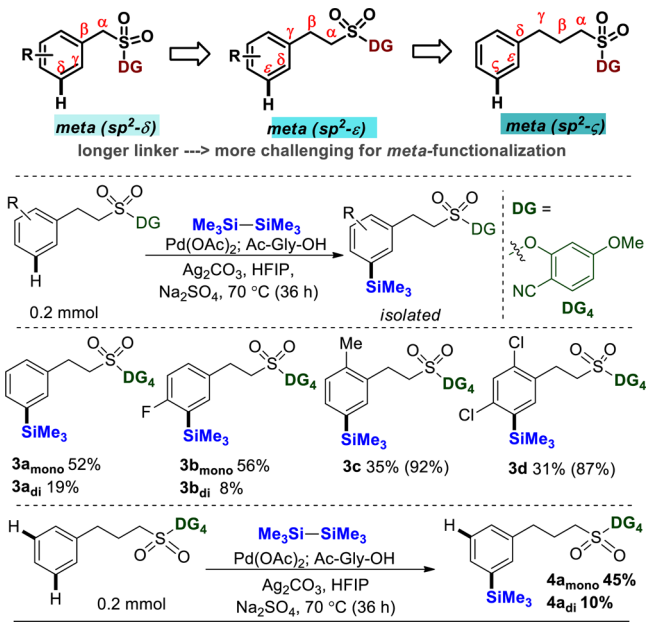
Table 3. Scope of Silylation on Benzylsulfonic Acid Derivatives[b,18]





[a]72 h, 45 °C. [b]Reaction conditions: $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), Ag_2CO_3 (3 equiv), dry HFIP (1.8 mL), anhydrous Na_2SO_4 (200 mg), hexamethyldisilane (sequential addition). Yields in parentheses are based on recovered starting materials;

Table 4. Silylation on 2-Phenylethanesulfonic Acids (sp^2-ε) and 3-Phenylpropane-1-sulfonic Acid (sp^2-ζ)[a,18]



[a]Reaction conditions: $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), Ag_2CO_3 (3 equiv). dry HFIP (1.8 mL), anhydrous Na_2SO_4 (200 mg), hexamethyldisilane (4 equiv). A sequential addition of $Pd(OAc)_2$ (5 mol %) and hexamethyldisilane (2 equiv) was carried out after 24 h. Yields in parentheses are based on recovered starting materials.

Table 5. Silylation on Benzylsulfonic Acid with Other Disilanes[18]

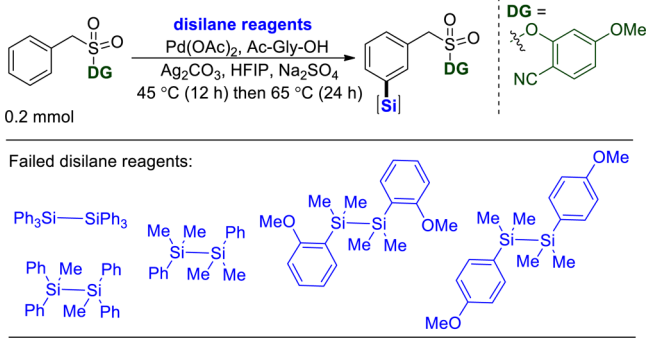
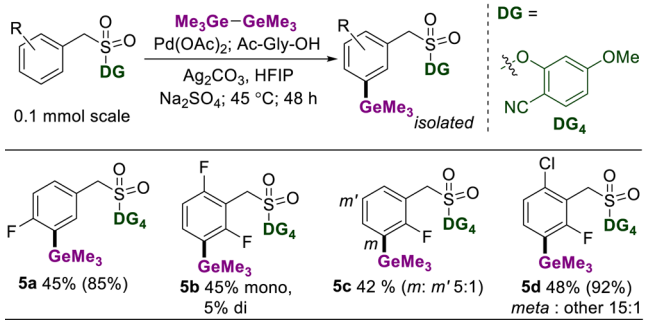


Table 6. Scope of *meta* Germanylation[a,18]



[a]Yields in parentheses are based on recovered starting materials.

similar to that of silylation. Despite the higher reducing property of the digermanium reagent and less stability of the C−Ge bond, we succeeded in generating the *meta*-germanylated product with moderate to good yields (**5a−d**, Table 6).

The synthetic utility of the current *meta* silylation was further demonstrated through three-way modification of the monosilylated product. First, employing the trimethylsilyl entity as a transformable group, C−I,[19] C−O,[20] and C−C[21] bonds were formed (Scheme 3, **7a−c**). As a direct synthetic route for preparing *meta*-heteroarylated arenes has yet to be reported, a two-step pathway to access these organic moieties through

DOI: 10.1021/acs.organomet.7b00309
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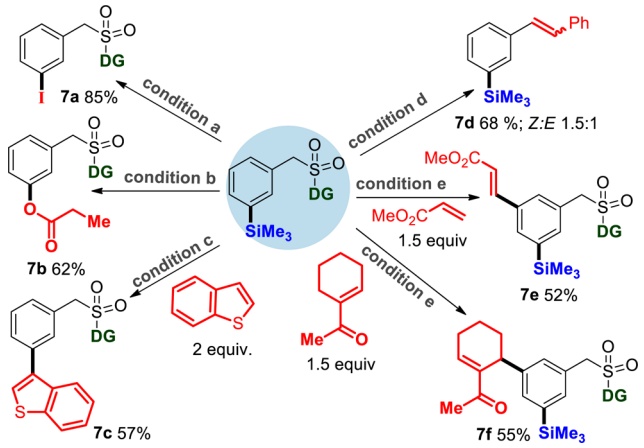
Scheme 3. Synthetic Diversification of *meta*-Silylated Product[a,18]

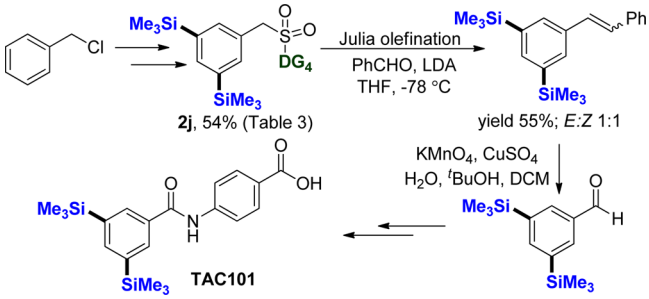


[a]Conditions: (a) $AgNO_3/I_2$; (b) $Pd(OAc)_2/PhI(OCOCF_3)_2/EtCO_2H$; (c) $Pd(MeCN)_2Cl_2/CuCl_2$; (d) PhCHO/LDA; (e) $Pd(OAc)_2$/Ac-Gly-OH/Ag_2CO_3.

meta-silylation followed by C−C coupling has immense significance (**7c**). Second, the synthetic applicability of the benzylsulfonate moiety was established by utilizing a Julia-type olefination reaction to afford the *meta*-silylated olefin (**7d**). Finally, the residual *meta*-C−H bond of the monosilylated benzylsulfonate was further olefinated with a trimethylsilyl entity present at the other *meta* position (**7e,f**).

The usefulness of this protocol was further revealed by applying our protocol judiciously for the formal synthesis of the anticancer drug molecule TAC101. A synthetic outline was proposed to achieve the target molecule starting from benzyl chloride, employing our silylation strategy as the key step (Scheme 4).

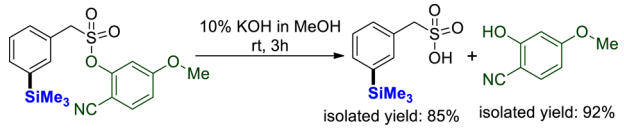
Scheme 4. Formal Synthesis of TAC101 from Benzyl Chloride



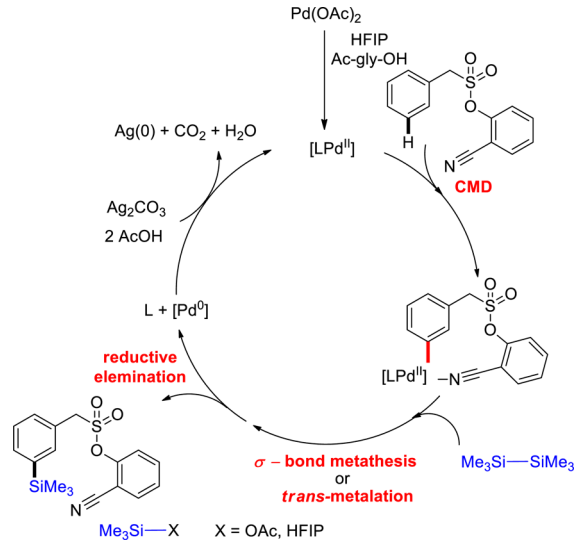
Moreover, the removal and quantitative recovery of the directing template was performed through the hydrolysis of the *meta*-silylated benzylsulfonate substrate (Scheme 5).

A plausible mechanism has been outlined in Scheme 6. At first palladium undergoes concerted metalation−deprotonation

Scheme 5. Removal and Recovery of Directing Template



Scheme 6. Proposed Mechanistic Cycle for *meta* Silylation



(CMD) reaction at the *meta*-C−H bond with the help of an amino acid ligand and HFIP solvent. Then hexamethyldisilane undergoes palladation through σ-bond metathesis or *trans*-metalation. Successive reductive elimination results in the *meta*-silylated product with concomitant formation of palladium(0). Next, palladium oxidizes to palladium(II) in the presence of the silver(I) salt. A detailed mechanistic study is currently underway in our laboratory.

CONCLUSION

In conclusion, we developed the first directing group assisted *meta*-C−H silylation protocol using hexamethyldisilane as the silylating agent. This silylation protocol was applied on benzylsulfonate esters along with 2-phenylethanesulfonic esters by overcoming the consequential strain energy related to a larger metallacycle. *meta*-Germanylation has also been achieved with synthetically useful yields and excellent selectivity for benzylsulfonate entities. The late-stage modification of a monosilylated entity was carried out to show the synthetic applicability. Additionally, a formal synthetic route was outlined for TAC101, a potential drug for lung cancer. These operationally simple reaction conditions with easily available silylating reagents are expected to have significance for broader applications in synthetic chemistry.[22]

EXPERIMENTAL SECTION

General Procedure A for Silylation through Remote *meta*-C−H Activation of Benzylsulfonic Acid Derivatives. In a clean, oven-dried screw-cap reaction tube, with previously placed magnetic stir bar, were placed substrate (0.2 mmol); $Pd(OAc)_2$ (0.1 equiv, 0.02 mmol, 4.5 mg); *N*-acetylglycine (0.4 equiv, 0.04 mmol, 4.5 mg), Ag_2CO_3 (3 equiv, 0.6 mmol, 166 mg), and anhydrous Na_2SO_4 (200 mg). Then hexafluoroisopropyl alcohol (1.8 mL) which was previously distilled and collected over activated 4 Å molecular sieves was added by syringe. Next, hexamethyldisilane (5 equiv, 1 mmol, 200 μL) was added to the mixture by syringe. The tube was tightly closed with the screw cap and placed in a preheated oil bath at 45 °C. After 12 h of vigorous stirring the reaction temperature was increased to 65 °C and 2 equiv of hexamethyldisilane (0.4 mmol, 80 μL) was added to the rection mixture. At time t = 24 h, another 1 equiv of hexamethyldisilane (0.2 mmol, 40 μL) was added to the reaction mixture and the mixture was stirred for another 12 h at 65 °C. The reaction mixture was cooled to room temperature and filtered through

DOI: 10.1021/acs.organomet.7b00309
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Celite. The reaction tube was washed with 10 mL of dichloromethane. The total organic portion was concentrated and purified via column chromatography through silica gel using petroleum ether and ethyl acetate as eluent.

General Procedure B for Silylation through Remote *meta*-C−H Activation of 2-Phenylethanesulfonic Acid Derivatives. In a clean, oven-dried screw-cap reaction tube, with a previously placed magnetic stir bar, were placed substrate (0.2 mmol), $Pd(OAc)_2$ (0.1 equiv, 0.02 mmol, 4.5 mg), *N*-acetylglycine (0.4 equiv, 0.04 mmol, 4.5 mg), Ag_2CO_3 (3 equiv, 0.6 mmol, 166 mg), and anhydrous Na_2SO_4 (200 mg). Then hexafluoroisopropyl alcohol (1.8 mL) which was previously distilled and collected over activated 4 Å molecular sieves was added by syringe. Next, hexamethyldisilane (5 equiv, 1 mmol, 200 μL) was added to mixture by syringe. The tube was tightly closed with the screw cap and placed in a preheated oil bath at 70 °C. At time t = 24 h, another 2 equiv of hexamethyldisilane (0.4 mmol, 80 μL) and $Pd(OAc)_2$ (0.05 equiv, 0.01 mmol, 2.2 mg) were added to the reaction mixture and the mixture was stirred for another 24 h at 45 °C. The reaction mixture was cooled to room temperature and filtered through Celite. The reaction tube was washed with 10 mL of dichloromethane. The total organic portion was concentrated and purified via column chromatography through silica gel using petroleum ether and ethyl acetate as eluent.

General Procedure C for Germanylation through Remote *meta*-C−H Activation of Benzylsulfonic Acid Derivatives. In a clean, oven-dried screw-cap reaction tube, with previously placed magnetic stir bar, were placed substrate (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv, 0.01 mmol, 2.2 mg), *N*-acetylglycine (0.2 equiv, 0.02 mmol, 2.2 mg), Ag_2CO_3 (3 equiv, 0.3 mmol, 83 mg), and anhydrous Na_2SO_4 (100 mg). Then hexafluoroisopropyl alcohol (0.9 mL) which was previously distilled and collected over activated 4 Å molecular sieves was added by syringe. Next, hexamethyldigermane (4 equiv, 0.4 mmol) was added to mixture by syringe. The tube was tightly closed with the screw cap and placed in a preheated oil bath at 45 °C. At time t = 24 h, another 2 equiv of hexamethyldigermane (0.2 mmol) and $Pd(OAc)_2$ (0.05 equiv, 0.005 mmol, 1.1 mg) were added to the reaction mixture and the mixture was stirred for 12 h at 70 °C. The reaction mixture was cooled to room temperature and filtered through Celite. The reaction tube was washed with 10 mL of dichloromethane. The total organic portion was concentrated and purified via column chromatography through silica gel using petroleum ether and ethyl acetate as eluent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.7b00309.

Optimization of reaction conditions, synthesis of the substrates, application, deprotection of acid moiety, characterization data, and ^{1}H NMR and ^{13}C NMR spectra of the compounds (PDF)

Accession Codes

CCDC 1528685 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare the following competing financial interest(s): A provisional patent on this work has been filed.

■ ACKNOWLEDGMENTS

This activity is supported by Science and Engineering Research Board, India. Financial support received from the CSIR (A.M.), UGC-INDIA (T.P.), and IIT Bombay (R.C. and S.R.) is gratefully acknowledged.

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(22) A provisional patent on this work has been filed.

DOI: 10.1021/acs.organomet.7b00309
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