Silicon–Tethered Strategies for C–H Functionalization Reactions

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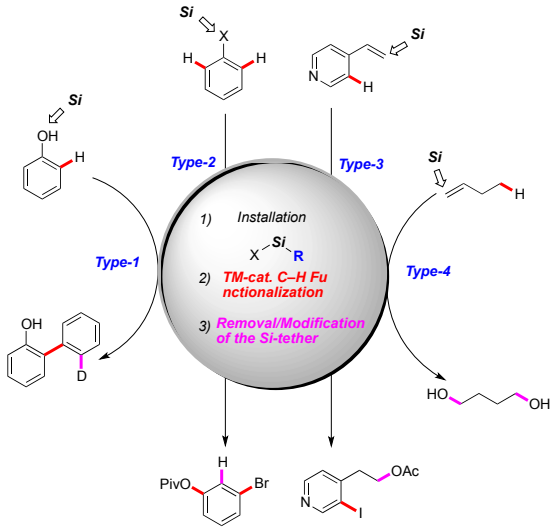
CONSPECTUS: Selective and efficient functionalization of ubiquitous C–H bonds is the holy grail of organic synthesis. Most advances in this area rely on employment of strongly- or weakly coordinating directing groups (DG) which have proven effective for transition metal-catalyzed functionalization of C(sp^2)–H and C(sp^3)–H bonds. Although, most directing groups are important functionalities on their own right, in certain cases, the DGs become static entities that possess very little synthetic leverage. Moreover, some of the DGs employed are cumbersome or unpractical to remove, which precludes the use of this approach in synthesis. It is believed, that development of a set of easily installable and removable/modifiable DGs for C–H functionalization would add tremendous value to the growing area of directed functionalization, and hence would promote its use in synthesis and late-stage functionalization of complex molecules. In particular, silicon tethers have long provided leverage in organic synthesis as easily installable and removable/modifiable auxiliaries for a variety of processes, including radical transformations, cycloaddition reactions, and a number of TM-catalyzed methods, including RCM-, and cross-coupling reactions. Employment of Si-tethers is highly attractive for

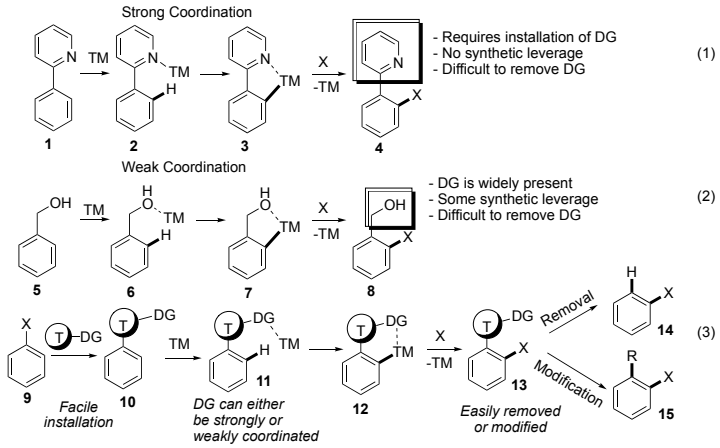
several reasons: 1) they are easy to handle/synthesize and are relatively stable; 2) utilize cheap and abundant silicon precursors; and 3) Si-tethers are easily installable and removable/modifiable. Hence, development of Si-tethers for C–H functionalization reactions is appealing not only from a practical, but also from a synthetic standpoint, since the Si-tether can provide an additional handle for diversification of organic molecules post C–H functionalization. Over the past few years, we developed a set of Si-tether approaches for C–H functionalization reactions. The developed Si-tethers can be categorized into four types: (Type-1) - Si-tethers possessing a reacting group, where the reacting group is delivered to the site of functionalization; (Type-2) - Si-tethers possessing a DG, designed for selective C(sp^2)–H functionalization of arenes; (Type-3) - reactive Si-tethers for C–H silylation of organic molecules; and finally, (Type-4) - reactive Si-tethers containing a DG, developed for selective C–H silylation/hydroxylation of challenging C(sp^3)–H bonds. In this Account, we outline our advances on the employment of silicon auxiliaries for directed C–H functionalization reactions. The discussion of the strategies for employment of different Si-tethers, functionalization/modification of silicon tethers, and the methodological developments on C–C, C–X, C–O, and C–Si bond forming reactions via silicon tethers will also be presented. While the work describe herein presents a substantial advance for the area of C–H functionalization, challenges still remain. The use of noble metals are required for the C–H functionalization methods presented herein. Also, the need for stoichiometric use of high molecular weight silicon auxiliaries is a shortcoming of the presented concept.



1. INTRODUCTION

Transition metal-catalyzed directed C–H functionalization is a highly important approach as it allows for selective conversion of ubiquitous C–H bonds into valuable C–C- and C–heteroatom bonds.[1] Typically, this has been accomplished by employment of *N*-based (pyridine, oxazolines, aminoquinoline, etc.) directed-groups (DG), which are strong σ-donors for electrophilic metals (Scheme 1, eq 1).[1] The coordinated complex **2** undergoes a cyclometalation event to adopt a favorable 5- or 6-membered metallacycle **3**, which is capable of reacting with electrophiles, nucleophiles, and/or oxidants to produce the C–H functionalized adducts **4**. Recently, Yu and co-workers introduced the employment of weakly coordinating oxygen based DGs (ketones, carboxylic acids, alcohols, and ethers) for C–H functionalization (**5**→**8**, Scheme 1, eq 2).[2] Often, DGs themselves are useful synthetic motifs. However, in cases where the DGs are redundant, and their removal is cumbersome or impractical, this approach becomes less attractive for synthesis. Thus, employment of easily installable (**9**→**10**), and removable/modifiable (**13**→**14, 15**), auxiliary for directed C–H functionalization (**10**→**13**), is appealing from both practical and synthetic standpoint (Scheme 1, eq 3).[3] Silicon tethers have long been recognized in organic

synthesis as easily installable and removable/modifiable auxiliaries for classical radical and cycloaddition reactions, as well as for a variety of TM-catalyzed transformations.[4] Over the past few years, we developed and employed removable/functionalizable silicon tethers bearing a DG for activation and functionalization of ubiquitous C–H bonds present in organic molecules. Our strategy empowered a facile C–H acetoxylation/pivaloyloxylation, hydroxylation, halogenation, arylation, alkenylation, alkylation, silylation, and carbonylation of C(sp^2)–H bonds. Most recently, we have also reported C–H silylation and desaturation of unreactive C(sp^3)–H bonds. In this Account, we outline our efforts on employment of silicon auxiliaries for directed C–H functionalization reactions. Strategies of employing different silicon tethers for various C–H functionalization, as well as functionalization/modification of the employed silicon tethers, will also be discussed.

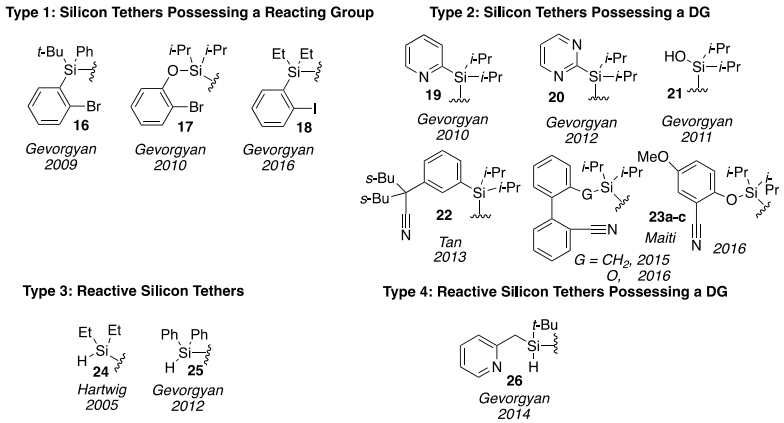


Scheme 1. Directing Group Concept for C–H Functionalization

2. DESIGN OF SILICON TETHERS

The developed Si-tethers for C–H functionalization can be categorized into four different types (Scheme 2). The first type involves Si-tethers possessing a reacting group, where the reacting group is delivered to the site of functionalization (Type 1). The second category (Type 2),

consists of Si-tethers, containing either a strongly coordinating *N*-based DG or weakly coordinating *O*-based DG. The third type (Type 3) features reactive Si-tethers, where the silicon tethers are incorporated at the site of functionalization, formally representing the C–H silylation. Lastly, the fourth type involves reactive Si-tethers containing a DG.

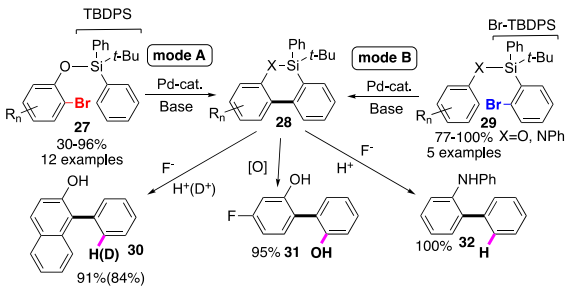


Scheme 2. Types of Silicon Tethers for C–H Functionalization

3. C(sp^2)–H FUNCTIONALIZATION VIA SILICON TETHERS

3.1. Type 1 Tethers: C–H Arylation

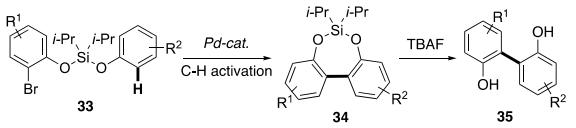
Efficient and selective C(sp^2)–H arylation toward biaryl systems is an important process due to the significance of these motifs in pharmaceutical and material sciences.[5] Intermolecular methods for the formation of biaryls often suffer from low efficiency and regioselectivity. In contrast, intramolecular versions are selective and efficient, however, they are limited to the formation of the tricyclic biaryl systems. In the model studies, we shown that biaryls can be accessed with the aid of the common TBDPS protecting group/tether as an efficient aryl group donor for *o*-bromophenols via the Pd-catalyzed intramolecular arylation (**27→28)**, followed by a deprotection step (Scheme 3, mode A).[6] Next, we designed Br-TBDPS protecting group as efficient aryl group donor (**29→28)** for simple phenols and anilines (Scheme 3, mode B). Due to



Scheme 3. C–H Arylation Using TBDPS and Br-TBDPS Tethers

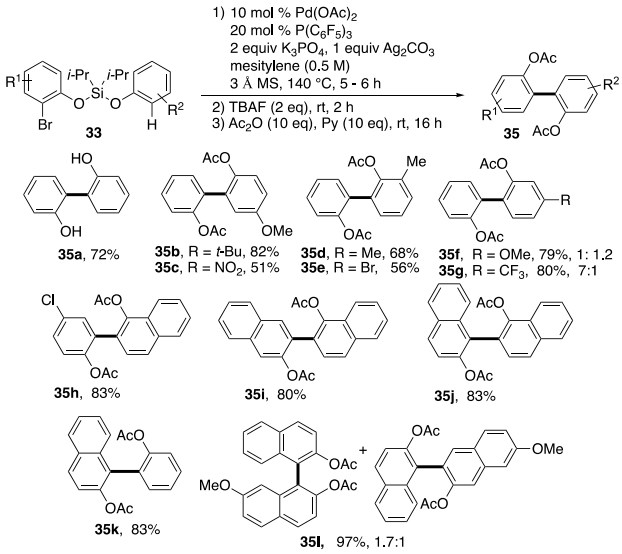
the modifiability of the silicon tether, the obtained biaryl silylcycle **28** can be further transformed into deuteriated biaryls (**30**), biphenols (**31**), or *o*-arylated anilines (**32**). The formation of biphenol adduct **31** is of particular synthetic interest since *ortho*-biphenol framework is a key unit found in many natural and synthetic bioactive molecules, and in various ligand families.[7] However, most of existing methods toward synthesis of these fragments involve harsh oxidizing conditions, employing toxic heavy metal oxidants, and are limited to formation of symmetrical and electron-rich systems.[8] The described strategy above (Scheme 3, **28→31)** provided a partial solution to the problem; however, oxidation of the C–Si bond still required harsh conditions, and was limited to the particular substitution pattern. Aiming at the development of milder and more general method toward unsymmetrical and electronically diverse biphenols, we thought of bypassing the challenging C–Si bond oxidation. Accordingly, an intramolecular C–H arylation of easily available bis-aryloxy silane (**33)** toward 7-membered silacycle **34** was examined (Scheme 4),[9] which would provide an easy route to biphenols **35** via a routine deprotection of the silyl tether (Scheme 4). Indeed, it was found that Pd-catalyzed intramolecular arylation of bisaryloxysilane **33** into silacycle **34**, followed by desilylation to form biaryls **35** proceeded in highly efficient manner. A semi-one-pot procedure from **33** to **35** resulted in the same overall

efficiency. For easiness of separation, most of biphenols were isolated as acetates. This method appeared to be general and efficient, regardless on the electronic properties of substituents at



Scheme 4. Synthesis of Biphenols via C–H Arylation Using Type 1 Silicon Tethers

either phenol ring (Scheme 5, **35a-h**). Expectedly, *meta*-substituted phenols produced mixtures of regioisomers, where the regioselectivity was governed by both electronics and sterics (**35f-g**). Notably, this protocol is also efficient for synthesis of binapthols (**35i-j**,**l**).

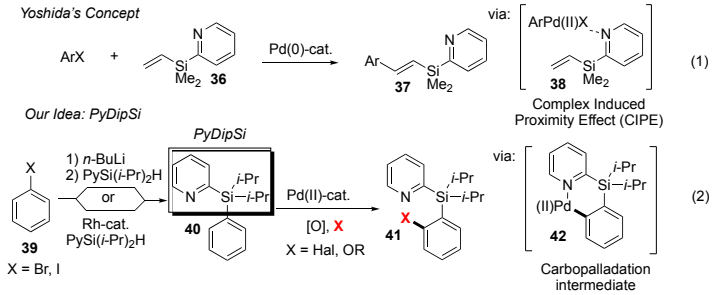


Scheme 5. Scope of Obtained Biphenols and Binaphthols

3.2. Type 2 Tethers: Directed ortho C–H Functionalization

In 2000, Yoshida introduced a vinyl 2-pySiMe$_2$ directing group for a regioselective intermolecular Heck reaction.[10] The observed high regioselectivity of the reaction was attributed to a complex-induced proximity effect (CIPE) enabling coordination of the pyridine moiety to

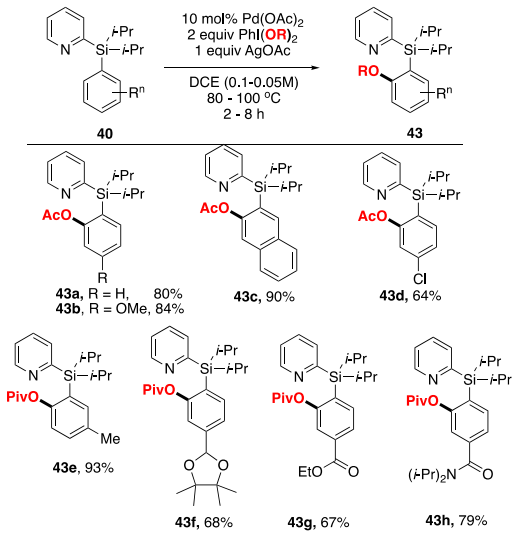
the electrophilic Pd-complex (**38**). Inspired by this observation, we hypothesized that the 2-pyridylsilyl group could serve as a removable DG for C–H functionalization. We envisioned that the pyridyl group could coordinate to an electrophilic Pd(II) species leading to the formation of a cyclometallated intermediate **42**, which would empower a C–H functionalization event, such as *o*-acetoxylation or halogenation reaction. However, employment of Yoshida's 2-pySiMe$_2$ group for C–H acetoxylation led to full decomposition of the substrate with no targeted oxygenation product observed. Upon optimization of the silicon tether, it was found that bis-isopropylsilyl group perfectly withstands the reaction conditions leading to highly efficient *o*-C–H acetoxylation reaction. Hence, the pyridyldiisopropylsilyl (PyDipSi) directing group, which soon became a DG of choice for various C–H functionalization reactions (*vide infra*), was born![11] The PyDipSi DG can efficiently be installed via quenching aryl organolithium species, derived from aryl halides, with commercially available 2-(diisopropylsilyl)pyridine; or via direct Rh-catalyzed coupling of aryl halides with 2-(diisopropylsilyl)pyridine (Scheme 6, **39→40**). The scope of C–H acetoxylation reaction using PyDipSi DG is depicted in Scheme 7. Both, acetoxylation- and pivaloxylation (**43e**) reactions



Scheme 6. Concept of PyDipSi Directing Group

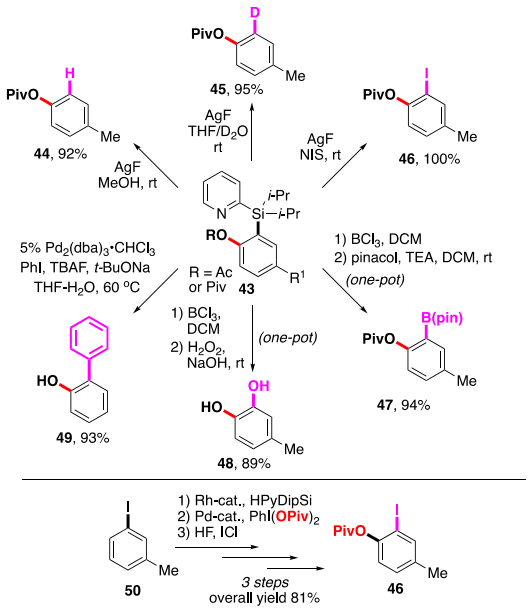
proceeded equally efficiently. Substrates possessing sensitive functionalities, such as pinacol-protected aldehyde (**43f**), CO_2Et (**43g**), and $CON(i\text{-}Pr)_2$ (**43h**), reacted well. After the scope of

this oxygenation reaction was established, further transformations of removable/modifiable PyDipSi group were performed (Scheme 8). It was found that the reaction of **43e** with AgF in



Scheme 7. Scope of C–H Acyloxylation of PyDipSi Arenes

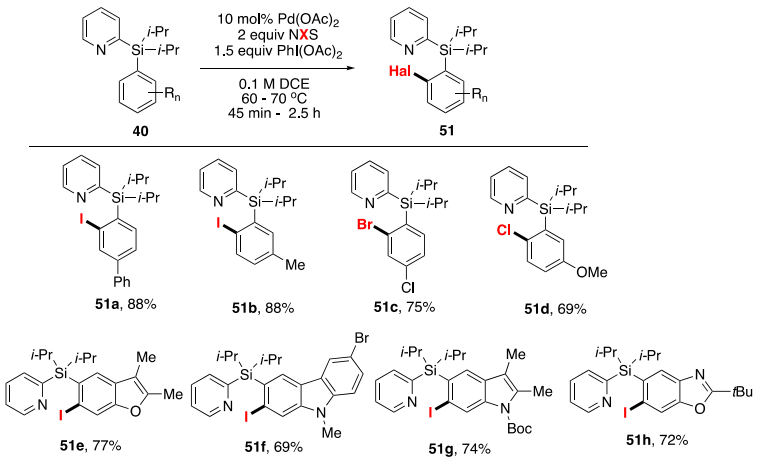
methanol resulted in efficient deprotection of the directing group, affording tolylpivalate **44** in 92% yield. Moreover, treatment of **43e** with AgF in THF/D_2O produced the deuterated arylpivalate **45** in 95% yield. Remarkably, a combination of AgF/NIS allowed for a quantitative



Scheme 8. Further Transformations of Obtained Acyloxy PyDipSi Arenes

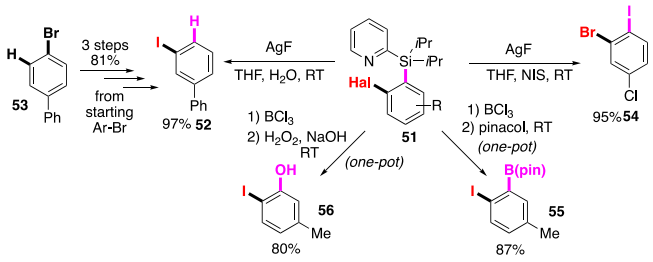
conversion of the PyDipSi group into iodide functionality (**46**). The latter transformation, taken together with the installation and pivaloxylation steps, represents a formal efficient 3-step *ortho*-oxygenation of 3-iodotoluene (**50**→**46**). Furthermore, **43e** was converted into synthetically valuable arylboronate **47** in 94% yield via a one-pot borodesilylation with BCl_3/protection with pinacol sequence. In addition, borodesilylation of **43e**, followed by oxidation, produced substituted catechol **48** in excellent yield. Finally, it was found that the acetoxy-derivative **43a** underwent an efficient Hiyama-Denmark cross-coupling with phenyl iodide and subsequent hydrolysis of acetoxy-group, providing 2-phenylphenol **49** in 93% yield (Scheme 8).

Next, employment of traceless/modifiable PyDipSi DG was successfully engaged in C–H halogenation of arenes (Scheme 9). Thus, C(sp^2)–H chlorination, bromination, and iodination were all achieved in good yields.[12] Notably, efficient iodination of molecules possessing electron-rich heterocycles such as furans, indoles, carbazoles, and oxazoles, was accomplished (**51e-h**). Markedly, the obtained halogenation adducts are inherently ambiphilic. Hence, a plethora of transformations can be envisioned by taking advantage of the nucleophilic and



Scheme 9. Scope of C–H Halogenation Reaction Employing PyDipSi DG

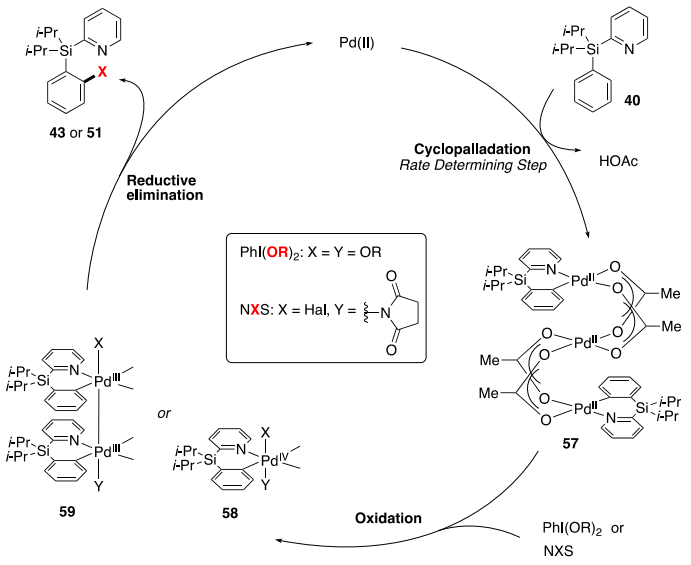
electrophilic nature of the C–Si and the formed C–X bond, respectively (Scheme 10). Indeed, the reaction of **51a** with AgF in THF/H_2O resulted in efficient deprotection of the directing group, affording *m*-iodobiphenyl **52** in 97% yield. Interestingly, the overall three-step transformation of *p*-bromobiphenyl into *m*-iodobiphenyl constitutes the first example of a formal sterically-controlled halogen dance reaction (**53** → **52**). Next, the iododesilylation reaction of chlorobromoarylsilane **51c** with NIS in the presence of AgF in THF allowed for efficient preparation of 1-chloro-3-bromo-4-iodobenzene (**54**), a synthetically useful and versatile building block for modular functionalization of the benzene ring. Furthermore, iodoarylsilane **51b** was efficiently converted into *o*-iodoarylboronate **55**, another powerful 1,2-ambiphile, in 87% yield via a one-pot sequence involving borodesilylation with BCl_3, followed by protection with pinacol. In addition, borodesilylation of **51b** followed by oxidation with H_2O_2/NaOH afforded *o*-iodophenol **56** in 80% yield.



Scheme 10. Scope of C–H Halogenation Reaction Employing PyDipSi DG

After extensive mechanistic studies, such as KIE and stoichiometric experiments,[13] it was proposed that the PyDipSi-directed C–H functionalization reactions proceed via the following mechanism (Scheme 11). $Pd(OAc)_2$ first reacts with arylsilane **40** affording the trinuclear Pd(II) complex **57** via a cyclopalladation process. A subsequent oxidation of Pd(II) in trinuclear species **57** with *N*-halosuccinimides or hypervalent iodine(III) reagents provides higher oxidation state

Pd species **58** or **59**. Finally, a reductive elimination affords the functionalization products and regenerates the active Pd(II) catalyst. The feasibility of the proposed steps was



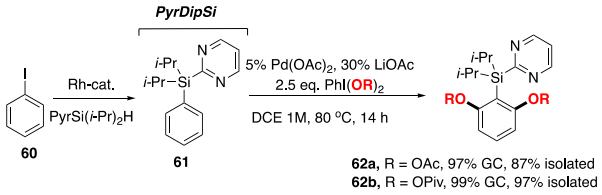
Scheme 11. Proposed Mechanism of C–H Acyloxylation Reaction Employing PyDipSi DG

supported by stoichiometric studies employing independently prepared trinuclear species **57**, which upon reaction with **40** was transformed into product **43**.[14] The observed high values of primary KIEs (k_H/k_D = 6.7) suggest that the breakage of C–H bond is a rate-limiting event in this transformation.

3.2. Type 2 Tethers: Double-Fold C–H Functionalization Reactions

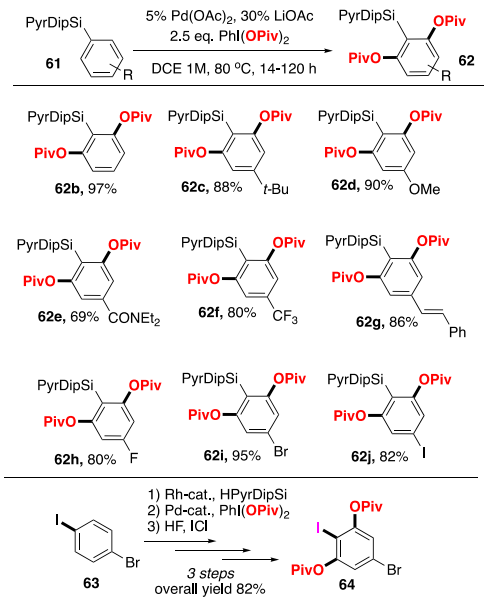
As outline above, using the developed PyDipSi DG allowed for efficient and selective Pd-catalyzed *mono* C-H oxygenation reaction of arenes. Notably, no double C–H functionalization products were observed throughout the course of initial studies. Aiming at the development of removable/modifiable DG which would allow for a double C–H functionalization event, we screened a number of potential Si-tethered DGs. It was found that the pyrimidine-based group (PyrDipSi), easily installed via the Rh-catalyzed silylation of aryl iodides with 2-

(diisopropylsilyl)pyrimidine (**60→61**), empowered a double-fold C–H acetoxylation event (Scheme 12, **61→62**).[15] Due to low stability of the produced bis-acetoxylated product **62a** during



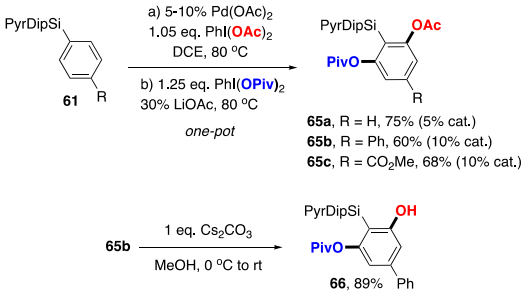
Scheme 12. Double-Fold C–H Acyloxylation Reactions Using PyrDipSi DG

the column-chromatography, we switched to more stable bis-pivaloxylated derivative (**62b**). Importantly, employment of LiOAc was curial for the success of the second C-H oxygenation event, which indicates that the reaction follows a concerted metalation-deprotonation (CMD) pathway.[16] The scope of this symmetrical double-fold C–H oxygenation methodology was found to be quite general, as substrates possessing both electron donating and -withdrawing substituents produced their respective symmetrical bis-pivaloxylated products in excellent yields (Scheme 13). It is believed that the efficient formal 3-step bis *o,o'*-oxygenation of 4-iodo-



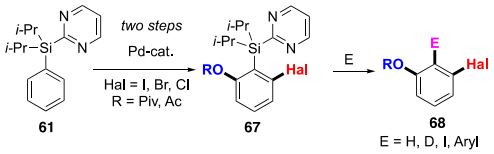
Scheme 13. Symmetrical Double-Fold C–H Pivaloxylation Reaction Using PyrDipSi DG

bromobenzene (**63→64**) via this approach represents a novel type of synthetic disconnection. Next, the possibility of a non-symmetrical bis-functionalization of PyrDipSi arenes via a sequential C–H acetoxylation/pivaloxylation reaction was examined (Scheme 14). It was found that acetoxylation of PyrDipSiAr **61a-c** with $PhI(OAc)_2$, followed by a *one-pot* pivaloxylation reaction of the intermediate using $PhI(OPiv)_2$ in the presence of LiOAc (30%), furnished the orthogonally protected resorcinol derivatives **65a-c** in good yields. As expected, the acetyl group could selectively be cleaved in the presence of pivaloxy group, thus producing mono-protected resorcinol derivative **66** in high yield.

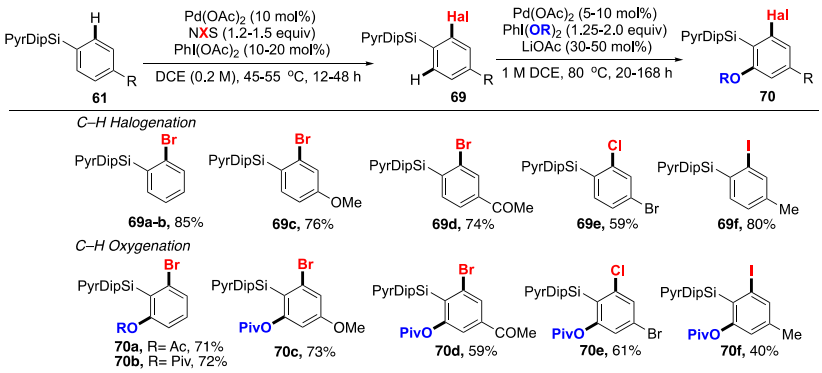


Scheme 14. Unsymmetrical Double-Fold C–H Pivaloxylation Reaction using PyrDipSi DG

After successful development of PyrDipSi DG toward symmetrical and unsymmetrical double-fold C–H oxygenation of arenes, we sought on translating this approach toward a sequential halogenation/oxygenation reaction, as it would provide efficient access to valuable *meta*-halophenols (**61→67→68**, Scheme 15).[17] Subjecting substrate **61** to the optimized halogenation conditions resulted in the *ortho*-brominated product **69** in excellent yield.



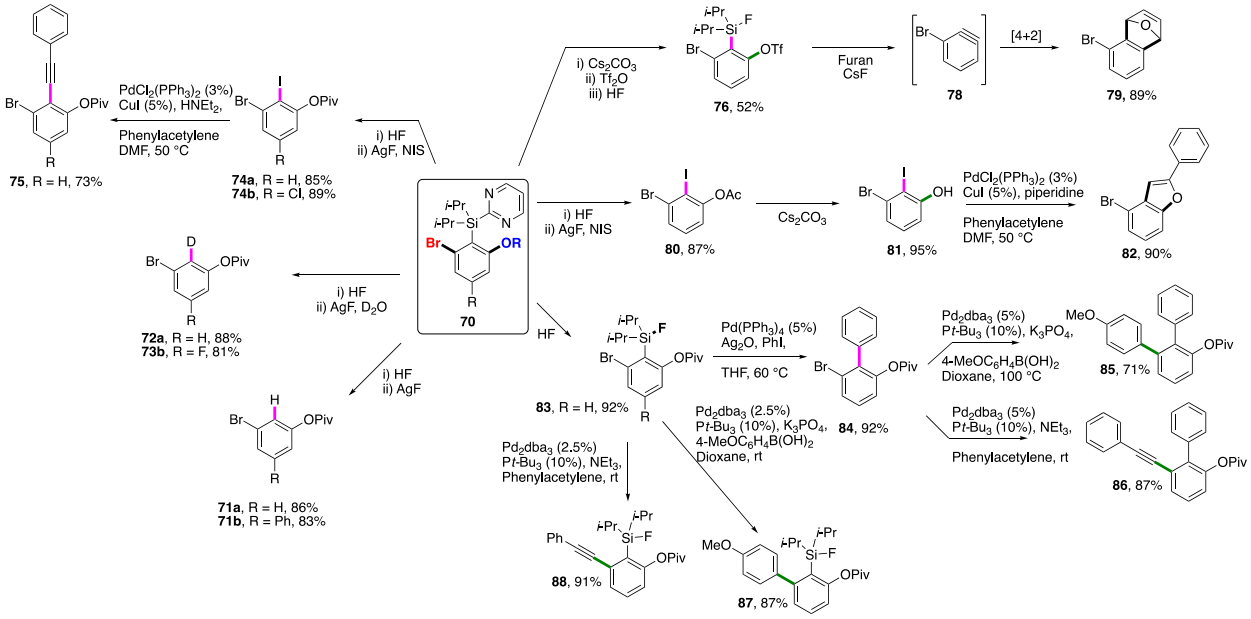
Scheme 15. Concept of Sequential C–H Halogenation/Oxygenation Using PyrDipSi DG



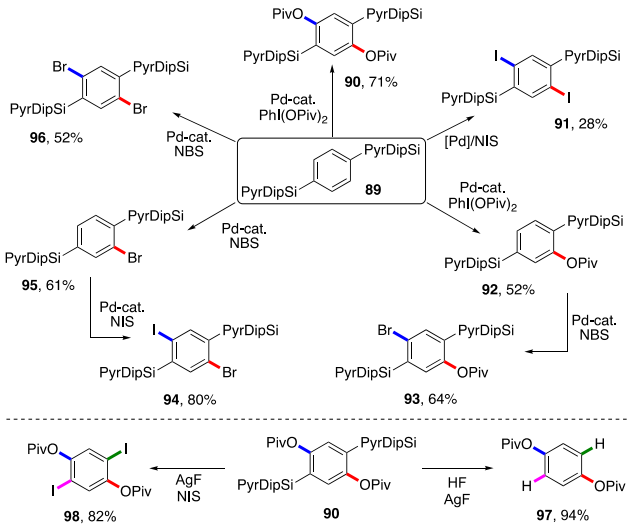
Scheme 16. Scope of Sequential C–H Halogenation/Oxygenation Using PyrDipSi DG

A subsequent exposure of **69** to the optimized C–H oxygenation conditions (*vide supra*) generated the unsymmetrically functionalized product **70** in good yield (Scheme 16). The scope of this protocol was successfully expanded to sequential C–H chlorination/pivaloxylation- as well as to C–H iodination/pivaloxylation reactions. In contrast to the traditional methods, which require multistep procedures, harsh conditions, and suffer from limited scope and low selectivity, the developed two-step protocol for synthesis of *meta*-halophenol derivatives features broad substrate scope, high functional-group tolerance, and mild reaction conditions. The obtained bis-functionalized adducts possess multiple independent handles for further functionalization, including the newly formed C–X and C–O bonds, as well as, the C–Si from the PyrDipSi DG (Scheme 17). Hence, a variety of transformations can be accomplished from building block **70** ranging from removal of the DG to form the *meta*-halophenol (**70**→**71**); sequential Hiyama-Denmark and Suzuki-Miyaura cross–coupling reaction via **70**→**83**→**84**→**85** to generate the corresponding trifunctionalized arene; and tosylation of the formed C–OPiv bond followed by benzyne formation and [4+2] cycloaddition reaction with furan to produce **79**. Moreover, we were able to utilize this tactic toward multisubstituted arenes with bis-PyrDipSi substrate **89**

(Scheme 18).[18] The formed symmetrically- (**90-91**, **96**) and unsymmetrically substituted (**93**, **94**) aryl silanes could serve as valuable building blocks for material- and supramolecular chemistry.



Scheme 17. Synthetic Utility and Further Transformations of Building Block 70

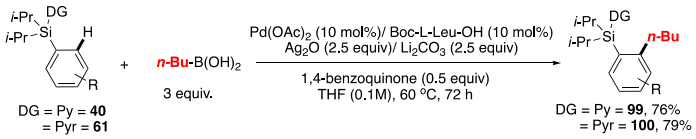


Scheme 18. Toward Multi-Substituted Arenes Employing Bis-PyrDipSi Substrate 89

3.3. Type 2 Tethers: C–C Bond Forming Reactions Using PyDipSi and PyrDipSi DGs

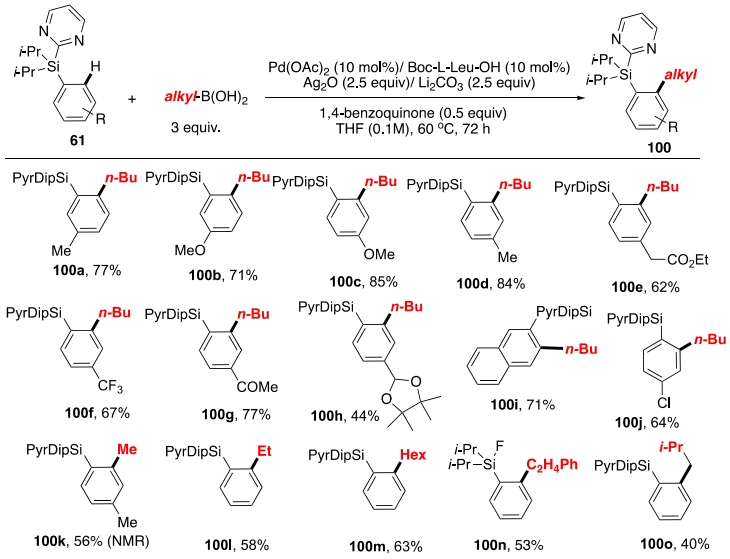
3.3.1. C–H Alkylation

We have also recently developed the Pd-catalyzed *ortho* C−H alkylation of arenes employing PyDipSi and PyrDipSi DGs (Scheme 19).[19] Under Yu's reactions conditions,[20] alkylation of PyDipSi-Ar **40** and PyrDipSi-Ar **61** occurred efficiently, resulting in 76% and 79% isolated of



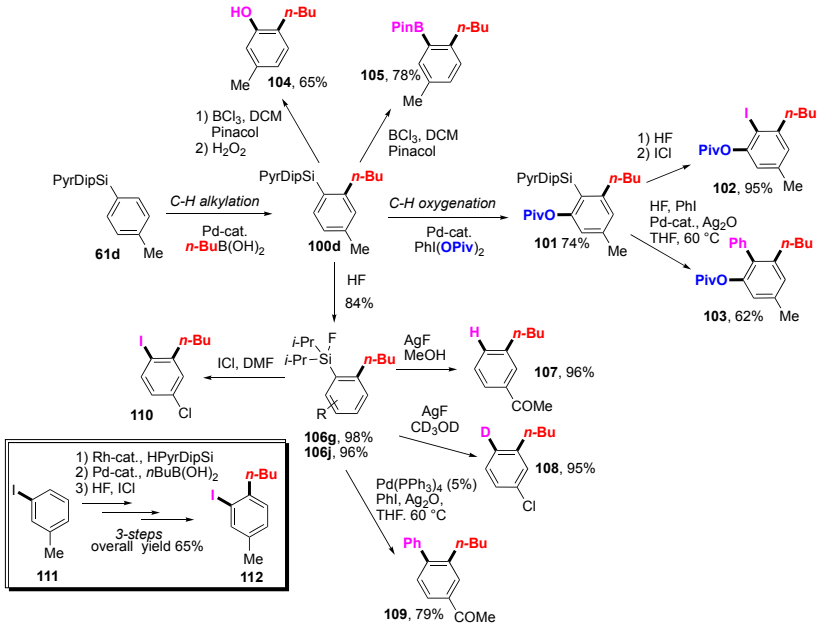
Scheme 19. C–H Alkylation Using PyDipSi and PyrDipSi DGs

99 and **100**, respectively. Although both DGs reacted equally well, due to easier isolation of the reaction products, the scope of this transformation was investigated using PyrDipSi DG (Scheme 20). Hence, aryl silanes (**61**) possessing *meta* substituents selectively underwent C–H alkylation at the less hindered site to produce **100a**,**b** in good yields. *Para*-substituted aryl silanes, containing various either electron-releasing or electron-withdrawing substituents reacted equally well (**100c-j**). Notably, this protocol allowed for efficient and selective C–H functionalization of arenes with other alkyl groups, such as methyl (**100k**), ethyl (**100l**), hexyl (**100m**), homobenzyl (**100n**)**,** and isobutyl (**100o**). We have also performed an unsymmetrical double-fold C−H



Scheme 20. Scope of Sequential C–H Halogenation/Oxygenation Using PyrDipSi DG

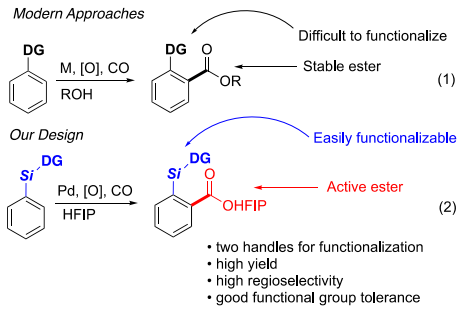
fuctionalization of PyrDipSi-arenes via a sequential C−H alkylation followed by a pivaloxylation reaction, where *meta*-alkylated phenols were obtained in good yield (Scheme 21, **100d→101**). In addition, a number of useful synthetic transformations involving removal and modification of the employed PyrDipSi DG into valuable alkyl-substituted arene building blocks were conducted (Scheme 21). The synthetic usefulness of the developed methodology could be exemplified by an efficient unprecedented 3-step conversion of 3-iodotoluene into the 3-iodo-4-butyltoluene (**111→112**).



Scheme 21. Synthetic Utility and Modification of PyrDipSi DG

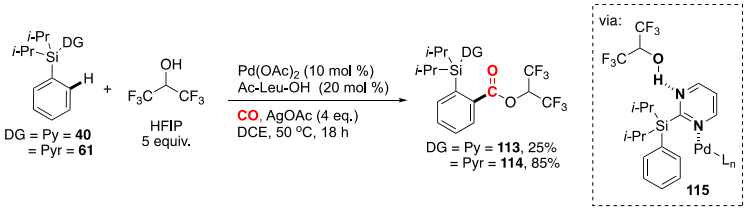
3.3.2. C–H Carbonylation

Directed C−H carbonylation reactions of arenes have become an increasingly important tool for synthesis of benzoates.[21] However, most developed methods thus far have been limited to synthesis of stable esters that are typically incompetent substrates toward their direct transformations (Scheme 22, eq. 1). Thus, we thought of developing a general method toward



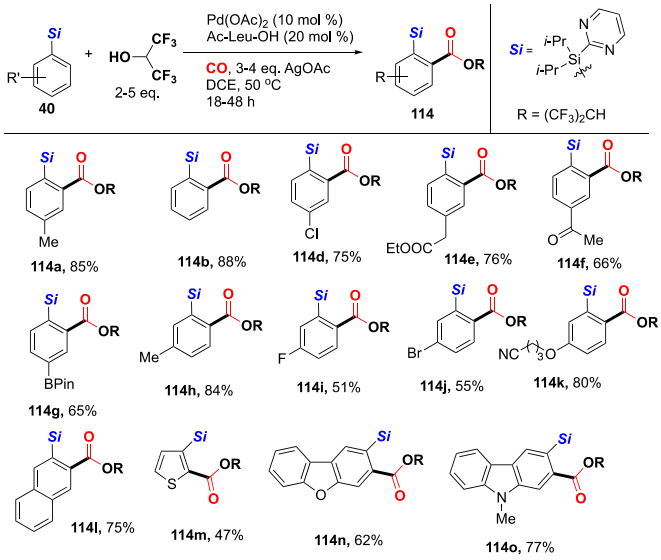
Scheme 22. Methods for C−H Alkoxycarbonylation

active benzoate esters using our traceless/functionalizable Silyl DGs.[22] Moreover, this approach will deliver privileged synthons bearing two independently modifiable sites (Scheme 22, eq. 2). After extensive optimization studies, it was found that under carbonylation reaction conditions in the presence of HFIP (hexafluoroisopropanol), PyDipSi-Ph **40** and PyrDipSi-Ph **61** produced the corresponding active esters **113** and **114** in 25% and 85% isolated yields, respectively (Scheme 23). Employment of other weak nucleophiles such as hexafluorophenol and *N*-hydroxyphthalimide were inefficient. Even addition of isopropanol, a nucleophilic analog of



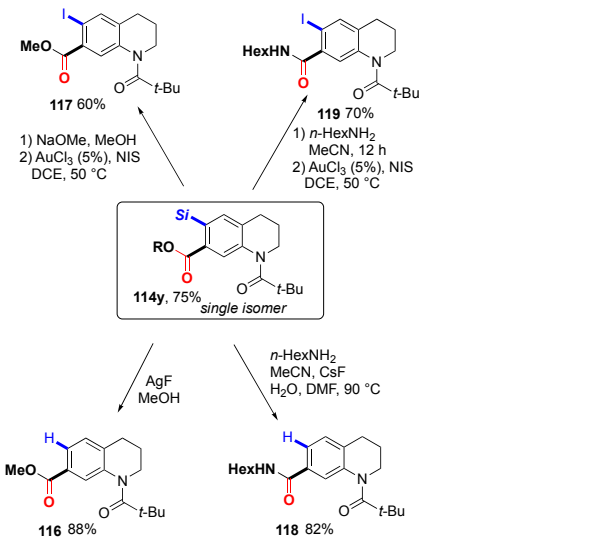
Scheme 23. Initial Studies for C−H Alkoxycarbonylation Using PyDipSi- and PyrDipSi-DGs

HFIP, failed to produce any ester products. Based on these observations, it became apparent that in this transformation HFIP plays a synergistic role with the employed pyrimidine based-DG. Indeed, ^{1}H-NMR studies revealed the presence of hydrogen bonding between HFIP alcohol and the pyrimidine nitrogen atom of the directing group (**115**), which is believed to have a double-



Scheme 24. Scope for C−H Alkoxycarbonylation Using PyrDipSi-DG

fold beneficial effect for this transformation by: (1) decreasing the basicity of the DG and thus enhancing its activity during the C–H activation event,[23] and, concurrently, by (2) increasing the nucleophilicity of the hydrogen-bonded HFIP alcohol.[24] This rationale provides the reason to the observation of lower reaction efficiency when a stronger coordinating PyDipSi DG was employed. The scope of this C−H alkoxycarbonylation reaction using PyrDipSi is illustrated in Scheme 24. The synthetic utility of the developed method was demonstrated on **114**, whose core is present in medicinally important compounds[25] (Scheme 25). Simple nucleophilic substitution reactions followed by one-pot protodesilylations or iododesilylations converted **114y** into the corresponding aryl ester **116**, iodo aryl ester **117**, aryl amide **118,** and iodo aryl amide **119**, in good to excellent yields.

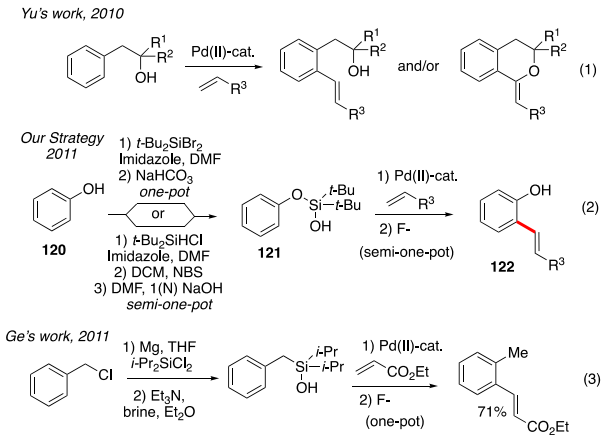


Scheme 25. Synthetic Utility of C−H Alkoxycarbonylation Using PyrDipSi-DG

3.4. Type 2 Tethers: C–H Functionalization Using Silanol DG

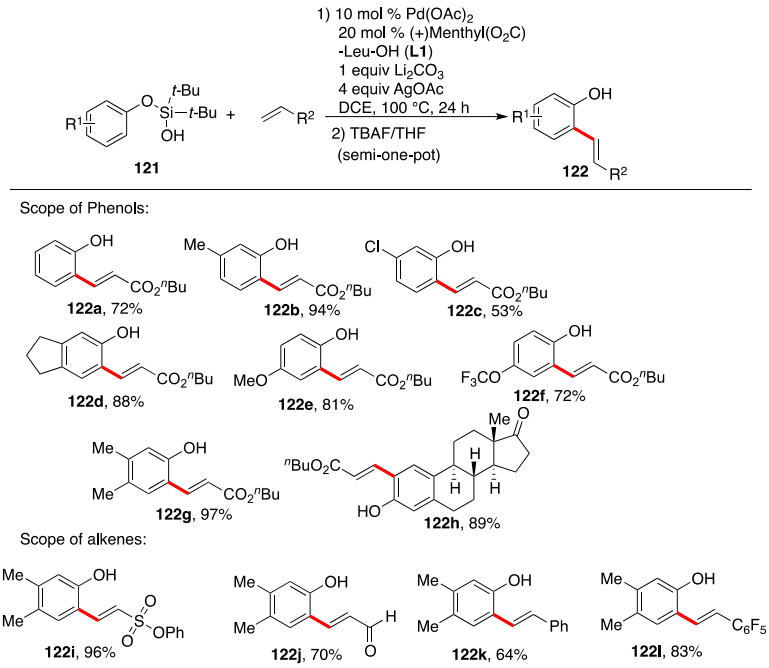
3.4.1. C–H Alkenylation

Yu reported C–H alkenylation of homobenzylic alcohols, where the alcohol serves as a weakly coordinating directing group.**Error! Bookmark not defined.** Considering similarity of OH group in alcohol and in silanol, we hypothesized that silanol can serve as a DG for Pd-catalyzed *o*-alkenylation of phenols (Scheme



Scheme 26. C−H Alkenylation Using Silanol DG

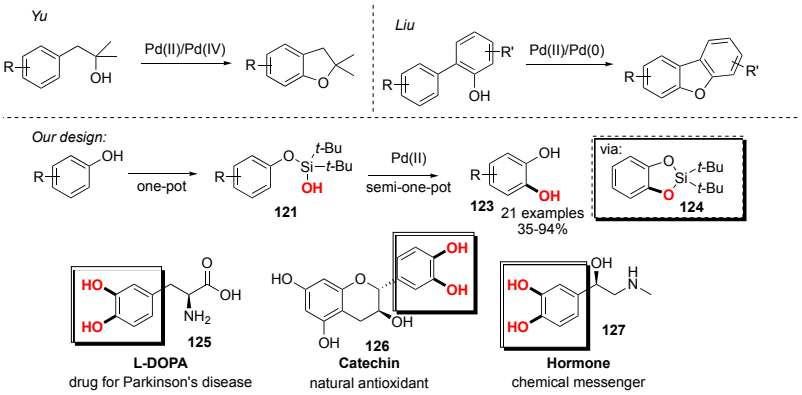
26). Our overall strategy involves a facile one-pot installation of the DG (**120→121**) followed by a semi-one pot Pd-catalyzed C–H alkenylation step, and a subsequent removal of the DG to furnish *o*-alkenylated phenols (**120→122**). [26] This transformation demonstrated broad scope with respect to the electronic nature of the phenols (**122a-l**, Scheme 27). Employment of various electron-deficient alkenes was most efficient, however, electron-rich alkenes were incompetent partners for this transformation. Later, Ge and co-workers extended this silanol DG concept for C−H alkenylation of toluene derivatives (Scheme 26, eq 3). [27]



Scheme 27. Scope of C−H Alkenylation Using Silanol DG

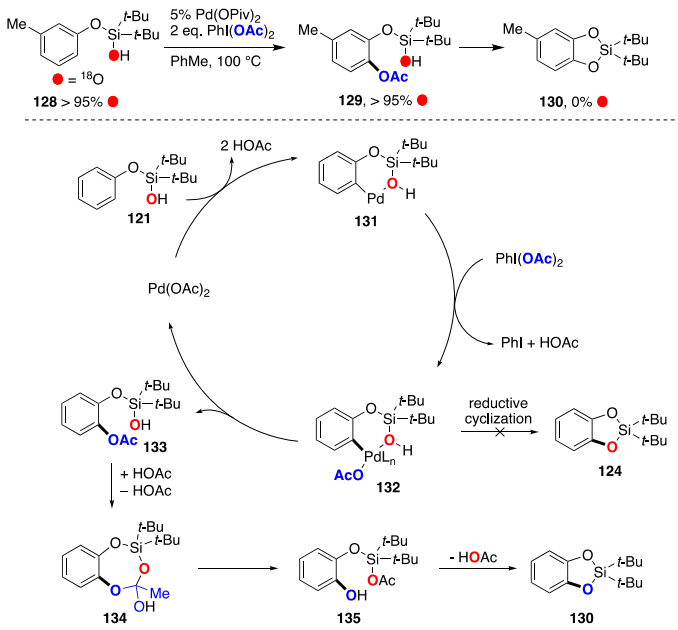
3.4.2. C–H Hydroxylation

The groups of Yu[28] and Liu[29] disclosed an intramolecular hydroxyl group-directed Pd-catalyzed oxygenation of arenes proceeding via a C–H activation/C–O cyclization protocol. We thought of employing the silanol DG for a formal semi-one-pot Pd-catalyzed C–H hydroxylation of phenols (**121→123**, Scheme 28), [30] which would allow for regioselective conversion of easily



Scheme 28. C−H Oxygenation Using Silanol DG

available phenols into biologically important catechol cores (**125-127**). Indeed, this transformation proceeded well, efficiently converting a wide range of diversely substituted phenols **121** into respective catechol **123**. Our initial assumption that the oxygen atom incorporated in the final product came from silanol **121** was disproved by ^{18}O-labeled studies. A careful monitoring of the reaction course starting from ^{18}O-labeled **128** revealed initial accumulation of the acetoxylated intermediate **129** followed by its conversion into the cyclized product possessing no ^{18}O label (**130**, Scheme 29). It deserves mentioning that throughout the reaction course the abundance of the ^{18}O label in both the starting silanol **128** and the acetoxylated product **129** remained unchanged. The mechanism of this oxygenation protocol is depicted in Scheme 29. First, $Pd(OAc)_2$ reacts with silanol **121** producing palladacycle **131**, in which the OH group from silanol acts as a neutral (L-type) ligand for Pd. Next, upon oxidation of **131**, the intermediate **132** is produced. A subsequent reductive elimination from **132** regenerates the Pd(II) catalyst and produces the acetoxylated intermediate **133**. The latter, presumably via an acid-catalyzed transesterification into **135** and a subsequent loss of acetic acid produces cyclic silyl-protected catechol **130**. Shortly after, we adopted this approach for C–H oxygenation of benzyl silanes.[31]

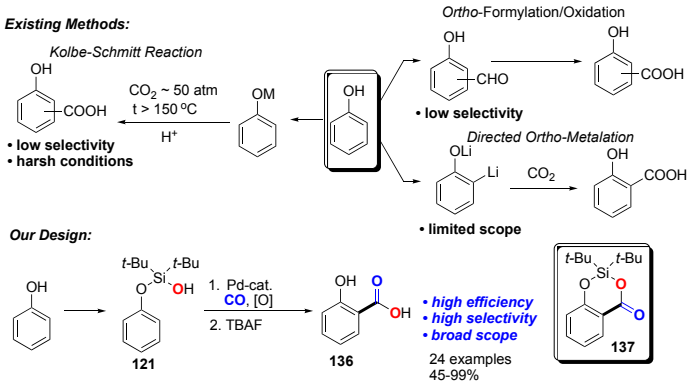


Scheme 29. Mechanism of C−H Oxygenation Using Silanol DG

3.4.3. C–H Carbonylation Reaction

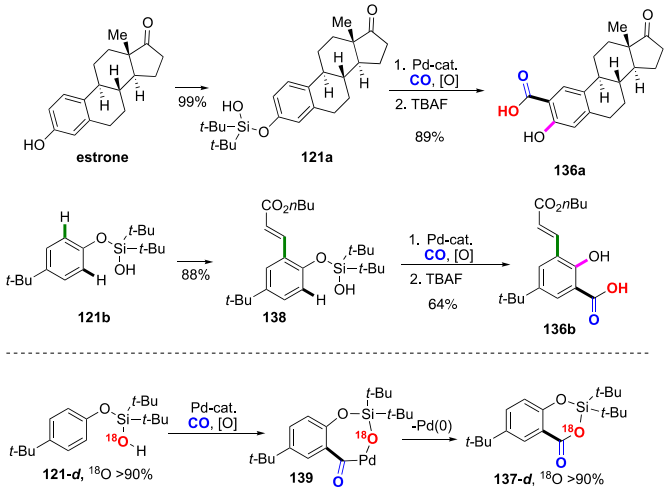
With the successful employment of silanol DG for directed C–H alkenylation and oxygenation reactions of phenols, we translated this approach to the Pd-catalyzed silanol-directed *ortho* C−H carboxylation reaction of phenols (**121**→**136**, Scheme 30) toward valuable salicylic acids derivatives via silacyclic intermediate **137**.[32] This strategy features milder conditions, boarder substrate scope, and higher regioselectivity compared to the state-of-the-art methods for synthesis of salicylic acids derivatives from phenols.[33] The synthetic potency of this method was showcased on functionalization of complex derivative **121a**, where the C–H carboxylation/desilylation occurred smoothly, producing **136a** as a single isomer in 89% yield (Scheme 31). In addition, an iterative C−H functionalization sequence involving silanol directed C–H alkenylation (**121b**→**138**), followed by the C–H carboxylation generated **136b** in good

overall yield. To the best of our knowledge, this represents the first example of a stepwise unsymmetrical C−H functionalization of phenols. Notably, in this transformation, contrary to the



Scheme 30. C−H Carbonylation Using Silanol DG

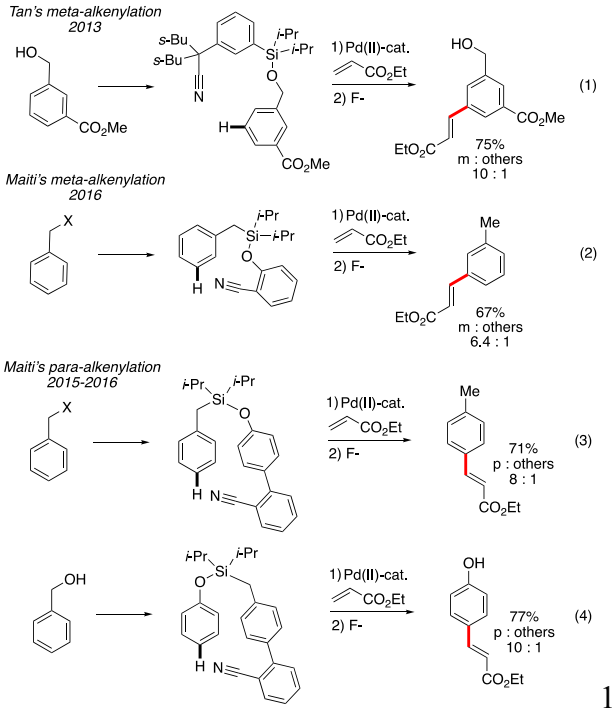
silanol-directed C–H oxygenation of phenols discussed above, the silanol serves as an anionic (X-type) ligand for Pd, thus delivering a silanol oxygen atom to the reaction product **136**, which was confirmed by the ^{18}O labeling studies (**121-*d*→139→137-*d***, Scheme 31).



Scheme 31. Scope of C−H Carbonylation Using Silanol DG

3.5. Type 2 Tethers: Directed Meta- and Para C–H Functionalization

The groups of Tan[34] and Maiti[35] have independently developed the type-2 nitrile-based silyl DGs (**22** and **23**, Scheme 2) for *meta*- and *para*- C–H functionalization of arenes, respectively, by merging Yu's nitrile-based DG for a remote C–H functionalization[36] with our temporary silyl

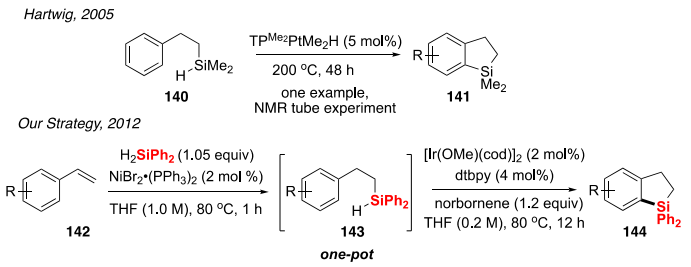


Scheme 32. Meta- and Para C–H Functionalization using Silicon Tethers

DG concept (Scheme 32). Both works feature broad substrate scope, high degrees of regioselectivity, as well as the possibility of the recovery and reuse of the silyl DG.

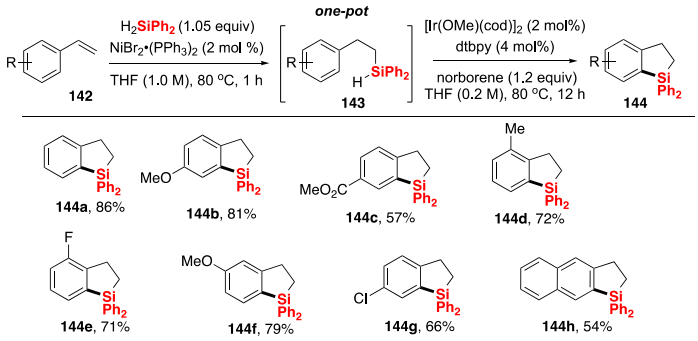
3.6. Type 3 Tethers: C–H Silylation of Arenes

Dehydrogenative coupling of the Si–H bond with aromatic C–H bonds is a powerful method for synthesis of valuable aryl- and heteroaryl silanes.[37] In 2012, we reported a practical and general *one-pot* procedure for synthesis of dihydrobenzosiloles **144** from styrenes **142** through the Ni-catalyzed hydrosilylation (**142**→**143**), followed by the Ir-catalyzed dehydrogenative cyclization



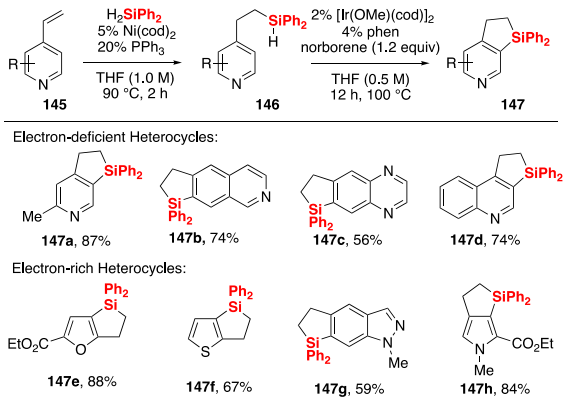
Scheme 33. One-pot Procedure for Synthesis of Dihydrobenzosiloles

(**143→144**, Scheme 33).[38] This work was inspired by Hartwig's work in 2005, where the possibility for the formation of dihydrobenzosilole from dimethylphenethylsilane via an intramolecular platinum-catalyzed dehydrogenative cyclization reaction was shown (**140→141**).[39] The scope of the developed transformation (**142→144**) was found to be quite general, as electronically diverse substituents at various positions of the arenes all reacted well producing the corresponding dihydrobenzosilole products in good yields (Scheme 34). Next, this



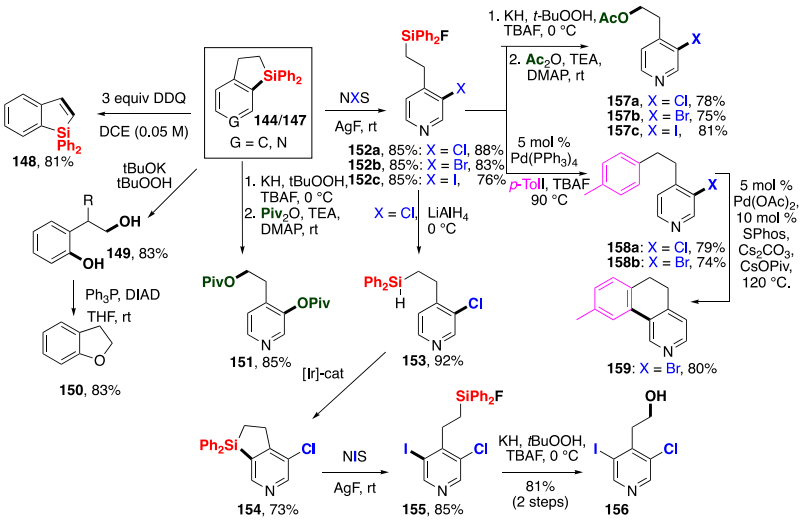
Scheme 34. Scope of Dihydrobenzosiloles via Hydrosilylation/Dehydrogenative Cyclization

method was extended to the heteroaromatic systems, however, in this case, a two-step protocol has been utilized (Scheme 35).[40] The scope of the reaction was found to be general, as silylation



Scheme 35. Hydrosilylation/Dehydrogenative Cyclization of Heteroarenes

of both electron deficient (**147a-e**) and -rich heteroarenes (**147e-h**) worked efficiently well. The synthetic utility of the obtained dehydrobenzosilols and their heteroaromatic analogs is illustrated in Scheme 36.

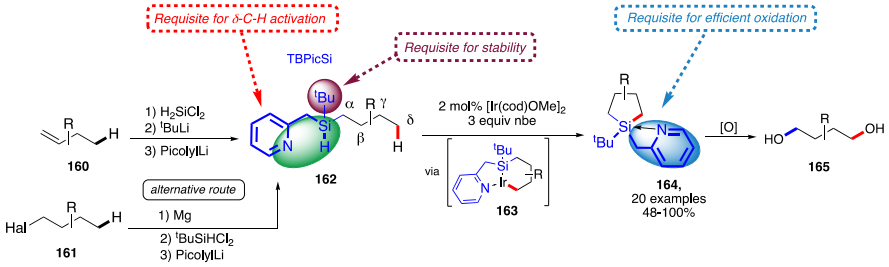


Scheme 36. Synthetic Utility of Dihydrobenzosiloles and their Heteroaromatic Analogs

4. C(sp^3)–H FUNCTIONALIZATION VIA SILICON TETHERS

4.1. Type 4 Tether: C–H Silylation using TBPicSi-DG

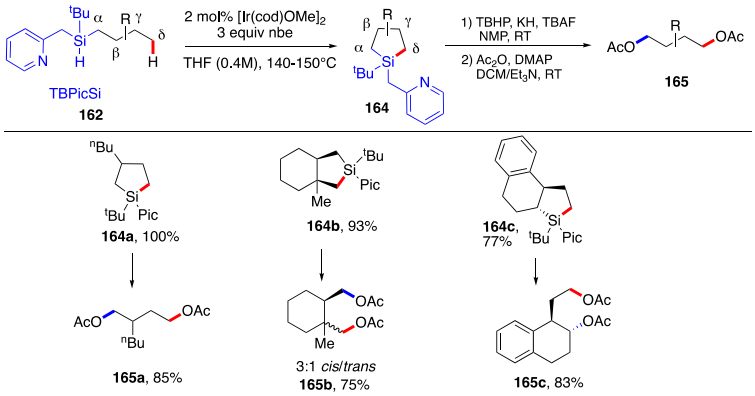
Site-selective functionalization of unactivated C(sp^3)–H has been the focus of many research group over the past years.[1] However, methods involving silicon tethers for activation of inert C(sp^3)–H bonds are quite rare. Recently, Hartwig reported γ-C–H silylation of primary and secondary bonds of alcohols (and ketones via hydrosilylation) employing type-3 tether **23** (Scheme 2) via intramolecular dehydrogenative Si−H/C−H coupling.[41] Other approaches usually rely on the use of strongly coordinating bidentate DGs and/or weakly coordinating groups, introduced by Daugulis[42] and Yu,[43] respectively. The former approach relies on the realization of a *N*,*N*-chelation, which was proven efficient for a remote TM-catalyzed aliphatic C−H activation



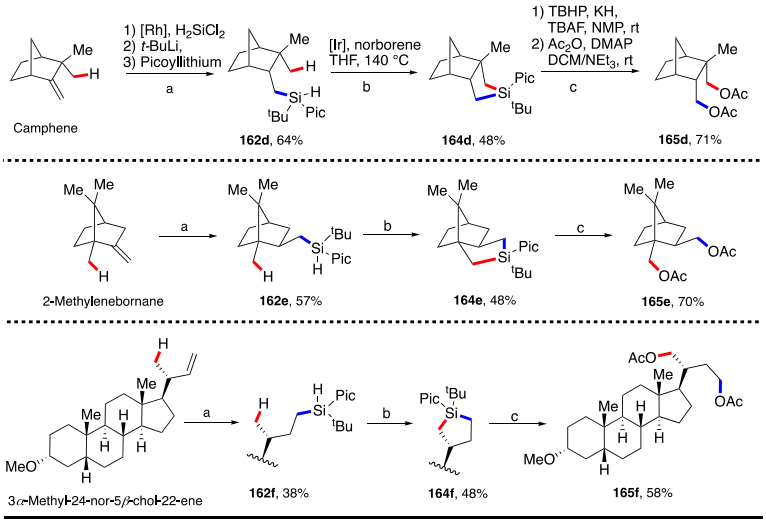
Scheme 37. δ-C(sp^3)−H Silylation/Oxygenation Using TBPicSi DG

reactions. Inspired by these works, we aimed at developing a new *Si*,*N*-type chelation-assisted auxiliary, which may empower a dehydrogenative Si−H/C−H dehydrogenative coupling event (Scheme 37).[44] It was found that employment of *tert*-butylpicolylsilicon **162** (TBPicSi, **26** Scheme 2) tether, installed via hydrosilylation of alkenes or by a Grignard addition from alkyl halides (**160/161→162**), enabled the desired dehydrogenative intramolecular silylation of δ-C(sp^3)−H bonds via **163**, producing dialkylsilolanes **164** in good yields. Notably, this represents the first example of δ-C–H silylation of aliphatics involving silicon tethers. The obtained 5-membered silanes were efficiently converted into 1,4-diols using Woerpel's oxidation procedure.

For convenience of isolation, the diols were isolated as diacetates (Scheme 38). Overall, this approach serves as a general method toward 1,4-diols from alkenes or alkyl halides. The



Scheme 38. Scope of δ-C(sp^3)−H Silylation/Oxygenation Using TBPicSi DG

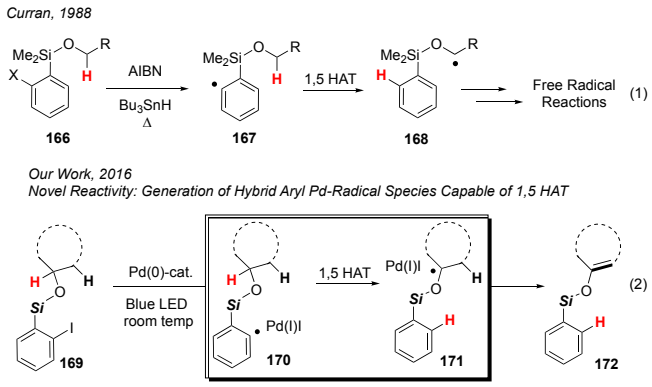


Scheme 39. δ-C(sp^3)−H Silylation/Oxygenation of Natural Products and Derivatives Using TBPicSi DG

synthetic potential of this methodology was showcased by late stage modification of complex natural products and derivatives (Scheme 39), where camphene, 2-methylenebornane, and the derivative of lithocholic acid were successfully converted into the respective 1,4-diols **165d-f**.

4.2. Type 1 Tether: Photocatalytic Desaturation of Silyl Ethers into Silyl Enol Ethers

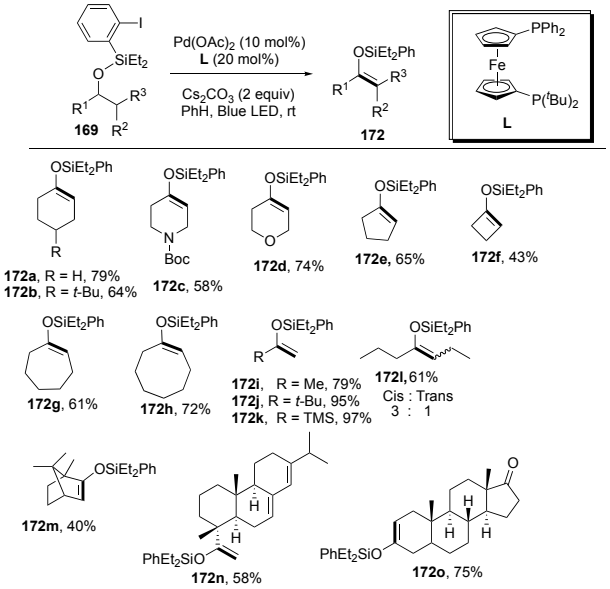
In 1988, Curran reported the possibility of activating the α-C(sp^3)−H position of silyl ethers via 1,5-HAT (**166→167**), where the radical species is transferred from the arylsilane to the remote C(sp^3)−H site (Scheme 40, eq 1).[45] Then, the alkyl radical **168** can engage in further reductive radical type reactions. We thought of developing an oxidative variant of Curran's free radical chemistry as potentially useful new method for a direct access of silyl enol ethers from easily available silyl ethers (**169→172**).[46] The success of this transformation would rely on the direct formation of a hybrid aryl Pd-radical complex **170** that is capable of a 1,5-HAT step (**170→171**) and a subsequent β-hydride elimination at the translocated site (**171→172**). It deserves



Scheme 40. Design of C–H Functionalization Using Tether 18 for Direct Oxidation of Silyl Ethers into Silyl Enol Ethers

mentioning that both steps (**169→170** and **170→171)** were unprecedented. In this proposed scenario, the silyl group is a Type-1 tether; however, the active hybrid Pd-radical species, rather than reacting group, is transferred to the remote site (see section 2). After extensive optimization work utilizing benchmark substrate **169a**, it was found that traditional thermal Pd-catalyzed conditions are not capable to trigger the planned transformation. Gratifyingly, irradiating this

reaction with visible-light under our previously reported Pd-catalyzed conditions[47] resulted in efficient formation of the desired silyl enol ether **172a**. Notably, this represents the first exogenous photosensitizer-free, visible light-induced Pd-catalyzed transformation. The scope of the transformation was quite broad as various cyclic, acyclic, and unsymmetrical silyl enols were efficiently converted into the silyl enol ethers with high yields and regioselectivity for α,β-desaturation (Scheme 41). Moreover, this desaturation method proved efficient in a more complex setting (**172m-o**), indicating its potential use for late stage modification of complex synthetic and natural molecules.



Scheme 41. Scope of the Photocatalytic Oxidation of Silyl Ethers into Silyl Enol Ethers

5. SUMMARY AND OUTLOOK

In this Account, we present our strategy toward site-selective C(sp^2)–H and C(sp^3)–H functionalization employing diverse designed silicon tethers. These silicon tethers, based on their role, are classified into different four categories (see section 2). In most cases, the silicon tethers themselves provide another handle for modification, where they can be routinely removed or

easily transformed into other useful functionalities. Applying this concept toward selective C(sp^2)–H functionalization has been well established, however, methods utilizing removable silicon tethers for C(sp^3)–H functionalization remains underexplored. One drawback for this concept is the use of high molecular weight stoichiometric silicon auxiliaries. Also, use of noble metals and high catalyst loading are often required to promote the C–H functionalization event. Hence, future directions will rely on the development of catalytic silicon tethers/DG and employment of abundant first-row transition metals for C–H functionalization of organic molecules.

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Notes

The authors declare no competing financial interest.

Biographical Information

Marvin Parasram was born and raised in the Bronx, New York. He received his BS degree in Chemistry from Stony Brook University in 2010. Later that year, he joined Prof. Vladimir Gevorgyan's group at the University of Illinois at Chicago as a Ph.D. student. During Ph.D. studies, he was involved in the development of novel Pd-catalyzed synthetic methodologies.

Vladimir Gevorgyan received his Ph.D. from the Latvian Institute of Organic Synthesis in 1984. After postdoctoral research (1992–1994, JSPS- and Ciba-Geigy International Fellowships) at Tohoku University, Japan, and a visiting professorship (1995) at CNR, Italy, he joined the

faculty at Tohoku University. In 1999, Prof. Gevorgyan moved to UIC as an Associate Professor. He was promoted to Full Professor in 2003. Since 2012, he is a Distinguished Professor of LAS. He is a Honorary Professor of St. Petersburg State University (2012), UIC University Scholar (2012), and Foreign Member of Latvian Academy of Sciences (2016). His group is interested in the development of novel catalytic synthetic methodologies.

ACKNOWLEDGEMENTS

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