Utilization of Silanols in Transition-Metal-Catalyzed Organic Synthesis

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ABSTRACT: The multifaceted implementation of silanols in organic synthesis is reviewed from the standpoint of developments in transition-metal-catalyzed reactions. The major properties of silanols are summarized according to the research fields that have utilized these intriguing species: silanols as nucleophiles to serve as bulky surrogates for water; silanols as temporary ligands to control regioselectivity of metal-catalyzed reactions and silanols as coupling partners for transferring functional groups. These topics are summarized to provide opportunities for future developments in the chemistry of silanols.

1. Introduction

1.1 General Physical Properties of Silanols

The origins of the research on silicon compounds bearing carbon–silicon bonds, namely organosilicon chemistry, can be traced back more than 150 years to the synthesis of tetraethylsilane by Friedel and Crafts in 1863.[1] A wide range of organosilicon compounds have been synthesized thus far. Among these compounds, organosilanols that possess one or more hydroxy groups on the silicon atom exhibit distinctive physical and reactive properties, so that this compound class has garnered considerable attention in the chemistry community.[2] This Introduction will discuss the similarities and differences between organosilanols and their carbon counterparts, carbinols.

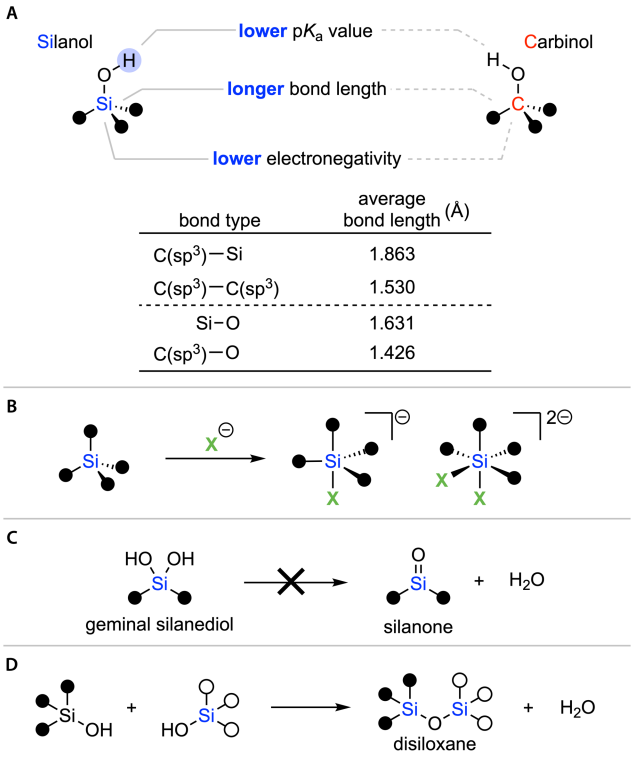
Organosilanols and carbinols have a similar tetrahedral core structure and different bond lengths around the core atom (Scheme 1A). The larger covalent radius of the silicon element renders the average bond length of C(sp^3)–Si (1.863 Å) about 20% longer than that of C(sp^3)–C(sp^3) (1.530 Å).[3] The average bond length to the oxygen atom, Si–O (1.631 Å), is about 15% longer than C(sp^3)–O (1.426 Å). These features allow the structure of the same connectivity pattern for silicon-substituted organic molecules as carbon-based ones. According to the Pauling scale, the electronegativity of silicon is 1.90 while that of carbon is 2.55.[4] This major difference results in a gap in bond polarity, which has a significant impact on reactivity through simple substitution of the atoms. The hydroxy groups of silanols are known to be more acidic than those of the corresponding carbinols because of the putative alpha effect of silicon.[5] Diverse reports on measurements of silanol pK_a values have appeared in literature.[6] In 1970, Kagiya reported the pK_a(H_2O) value of Me_3SiOH to be 11[6a] and Schindler reported in 1974 the pK_a(H_2O) value of Et_3SiOH as 13.63 ± 0.07,[6b] both much lower than that of *t*BuOH (pK_a(H_2O): 19). The pK_a(DMSO) value of Ph_3SiOH was initially reported to be 16.57 ± 0.11, which is lower only by 0.4 pK_a units than the reported pK_a(DMSO) value of Ph_3COH (16.97 ± 0.24).[6c] Soderquist later experimentally determined the pK_a(DMSO) value of *i*Pr_3SiOH using Bordwell's method.[6d] The reported

pK_a(DMSO) value is 24.4 ± 0.1, which is much lower than Bordwell's reference data for *t*BuOH (pK_a(DMSO) ~ 32.2). Franz reported the simulated pK_a values of silanols using a semi-empirical method with the aid of DFT calculations. The calculated pK_a(H_2O) values are 11.7 for Ph_3SiOH and 12.0 for $Me_2PhSiOH$, which are very reasonable pK_a(H_2O) values for silanols.[6e] These data collectively indicate the considerably higher acidity of silanols compared to their carbon counterparts.

Silanols typically exist as tetra-coordinate species with a tetrahedral silicon center. Organosilanes can be transformed into the one with higher-coordinate species such as penta-coordinate silicates, or under specific conditions, hexa-coordinate bis-silicate species (Scheme 1B).[7] This typical character of penta- or hexa-coordinate silicon species is not possible for carbon-based compounds. Additionally, the preference for forming a multiple bond differs between carbon and silicon atoms. The formation of double or triple bonds on the silicon atom is thermodynamically disfavored.[8] Geminal silanediols or silanetriols bearing two or three hydroxy groups on the silicon atom exist as stable species without forming silanones through the possible dehydration process (Scheme 1C). This phenomenon of preventing the formation of multiple bonds contrasts with the efficient dehydration of carbon-based geminal diols to afford stable ketones. Given these unique properties of silanols, the divergent utilization of these species as metabolically resistant bioisosteres that mimic carbinols or intermediary carbonyl hydrates has become a popular research topic.[9]

A significant concern in the synthesis of silanols is the intermolecular dehydrative dimerization to form disiloxanes, which can occur under both acidic and basic conditions (Scheme 1D).[10] To avoid the formation of disiloxanes, meticulous selection of reaction conditions is necessary. Even during the purification, careful handling of silanols is often required.

Scheme 1. Representative Physical Properties and Reactivities of Organosilanols.



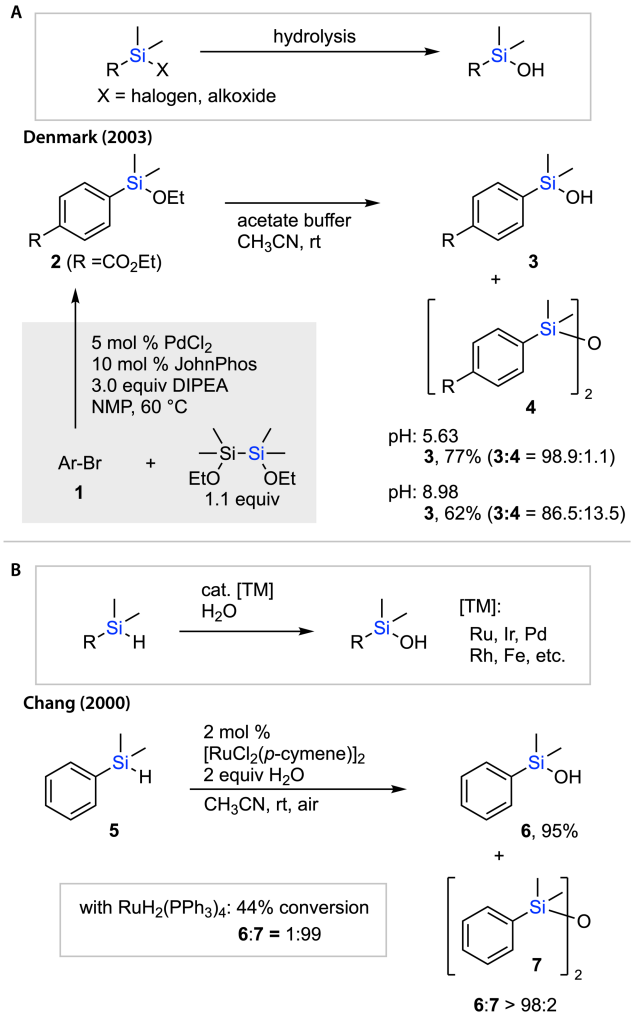
bond type	average bond length (Å)
C(sp^3)—Si	1.863
C(sp^3)—C(sp^3)	1.530
Si—O	1.631
C(sp^3)—O	1.426

1.2 General Synthetic Methods for Silanols

Organosilanols can be synthesized from various precursors. These diverse syntheses have been recently thoroughly reviewed,[2c,2d,2g] thus only the synopsis of the classical synthetic methods and the newest trend within the last five years are summarized in this section. One classical method for the synthesis of silanols is the hydrolysis of alkoxysilanes or halosilanes (Scheme 2A). In a typical example, alkoxysilane **2** synthesized by the silylation reaction of aryl bromide **1** with a diethoxydisilane can be hydrolyzed under slightly acidic buffered conditions (pH: 5.63) to provide arylsilanol **3** in good yield, accompanied by a trace amount of disiloxane **4**.[11] Thus, suitable hydrolytic conditions must be chosen to achieve the efficient hydrolytic synthesis of a variety of silanols. In certain instances, silanols are synthesized from the corresponding arylsilanes through a protodesilylation process, whereby the aryl groups are either directly transformed to hydroxy

group or first converted into fluoro- or alkoxysilanes as intermediates before subsequent hydrolysis.[12] Alternatively, silanols can be synthesized from hydrosilanes under oxidation conditions. Especially, transition-metal-catalyzed oxidation with oxygen sources enables to form silanols under neutral and mild conditions (Scheme 2B). Chang reported the Ru-catalyzed transformation of phenylsilane **5** into silanol **6** in excellent yield.[13] Under the optimized conditions using $[RuCl_2(p\text{-cymene})]_2$, the corresponding disiloxane **7** was generated only slightly. In contrast, the use of $RuH_2(PPh_3)_4$ as a catalyst resulted in only modest conversion of disiloxane **7** in modest conversion, highlighting the importance of the choice of metal catalysts for successful hydrolysis. Since silanols are slightly more acidic than carbinols, silanolates could be prepared in situ during the reaction. In the case that silanols are problematic on storage due to condensation sodium or potassium silanolate salts could be easily synthesized and isolated in almost pure form when NaH or KH are used as base.[2f]

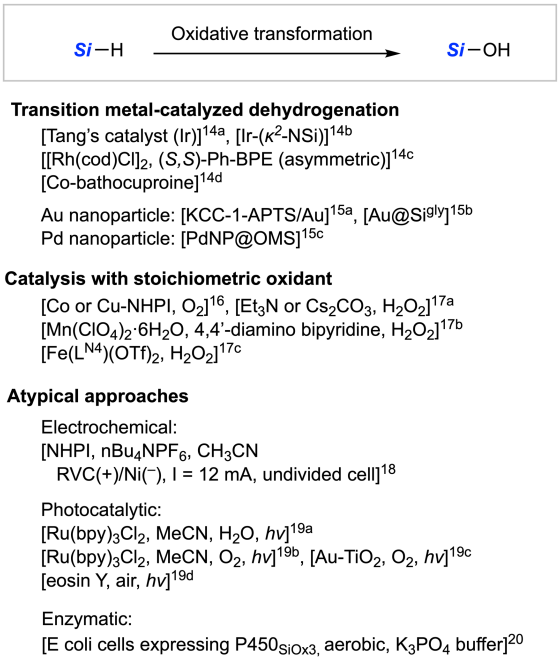
Scheme 2. Representative Preparation Methods for Silanols from Alkoxysilanes, Halosilanes, and Hydrosilanes.



In just the last five years, there has been a remarkable development in silanol synthesis, especially the oxidative transformations from hydrosilanes (Scheme 3). Among the recent additions to these oxidations are dehydrative coupling with water in the presence of metal catalysts[14] or metal nano particles[15]. Aerobic oxidation in the presence of transition metal catalysts is also updated to use a cobalt or copper-NHPI catalyst.[16] Oxidation in combination with hydrogen peroxide are newly reported.[17] The employed catalysts are organocatalyst or Cs base[17a], manganese catalyst[17b], iron

catalyst[17c]. Recent atypical approaches for silanol synthesis include the electrochemical transformation[18], while photocatalytic reactions are also widely employed.[19] As a new trend, Arnold recently reported an enzymatic oxidations of hydrosilanes using evolved enzyme.[20]

Scheme 3. Recent Advances (since 2018) of Synthetic Methods for Silanols from Hydrosilanes.

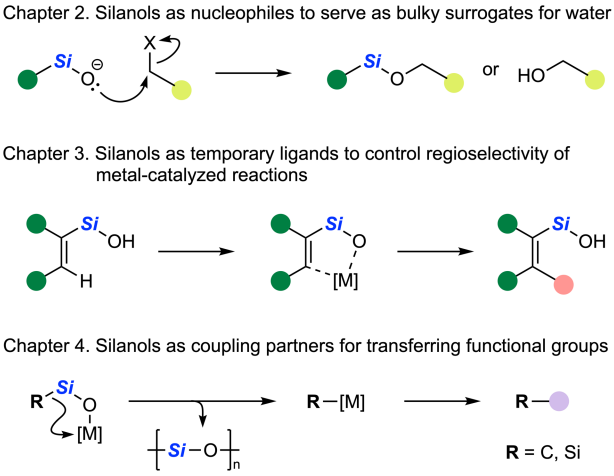


1.3 Scope of this Perspective

This Perspective will focus on the applications of organosilanols in transition-metal-catalyzed organic synthesis (Scheme 4). The utility of silanols as bulky nucleophiles as water surrogates is featured initially. Next, by leveraging the high coordinating ability of silanols to transition metal centers, the utility of silanols as ligand for intramolecular activation where the silanol unit remains after the reaction is described. Finally, this Perspective will feature the use of silanolates as a transformable functional group via C–Si or Si–Si bond activation, for which silanolates take

advantage of both the nucleophilicity and ligating ability to serve as donors for coupling reactions. This perspective will not discuss the broad application of silanols, especially silanediols or triols, for activation of hydrogen bond acceptors, which has already been thoroughly reviewed recently.[2g,21] Although silanolates holds an important position as useful ligands for transition metal catalyst, this Perspective will not deal with those where silanolate molecules are simply ligands and are not involved in any bond formation or cleavage.[22]

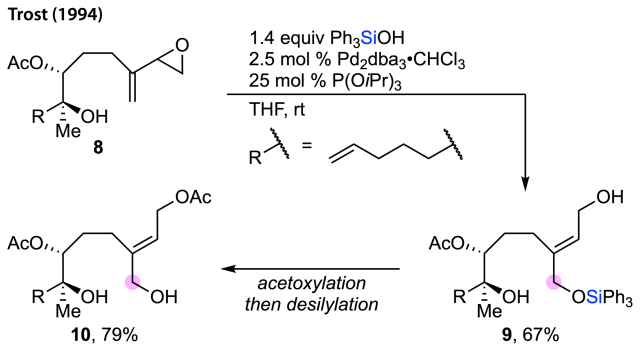
Scheme 4. Topics to be discussed in this Perspective.



2. Silanols as Nucleophiles to Serve as Bulky Surrogates for Water

Silanols are known as important nucleophilic reactants that are often used in catalytic reactions. The siloxy group, with a removable silicon unit, has high potential as a precursor for water equivalents or oxygen functional groups with different reactivity. While silanolates were previously only known as important reagents for hydrolysis,[23] Trost's pioneering work demonstrated their use in palladium-catalyzed allylic substitution reactions of allylic epoxide.[24] In general, the opening of epoxides with carbinols produces 1,2-dioxygen products. However, it was found that 1,4-dioxygenated products can be synthesized by using silanol as a nucleophile that can generate stable anions due to their bulkiness and higher acidity. This unique insight into the regioselectivity was also employed in the key step of the synthesis of (+)-(2'*S*,3'*R*)-zoapatanol.[25] Treatment of epoxide intermediate **8** with triphenylsilanol in the presence of a palladium catalyst affords 1,4-adduct **9** via the formation of silanolate in situ, followed by acetoxylation and subsequent desilylation to give diol **10** in good yield (Scheme 5).

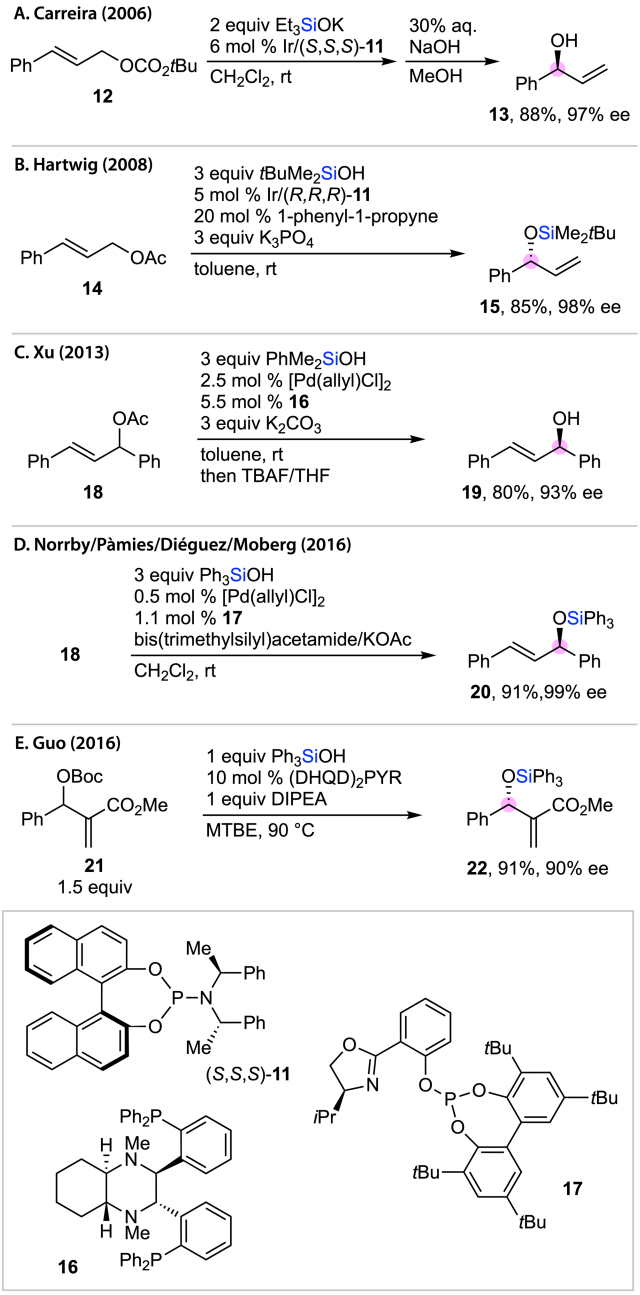
Scheme 5. Pd-catalyzed Allylic Substitution of Allylic Epoxide with Triphenylsilanol.



Nucleophilic silanols have been used in asymmetric catalysis since Carreira's report in 2006.[26] They showed that TESOK is an excellent nucleophile for asymmetric allylic etherification using iridium/phosphoramidite **11** catalyst (Scheme 6A). Chiral allylic alcohols can be synthesized

through desilylation under mild conditions with branched selectivity. Achiral allylic carbonate **12** is transformed to allylic alcohol **13** with excellent enantioselectivity. These results underscore the usefulness of silanolates as masked water nucleophiles. Hartwig found a reaction system that does not require the prior deprotonation of a silanol in a similar reaction using an iridium/phosphoramidite **11** catalyst in combination with K_3PO_4 (Scheme 6B).[27] Allylic acetate **14** could be converted to chiral allylic silyl ether **15** in good yield. By using a chiral bidentate phosphine ligand **16** or a chiral bidentate phosphinooxazoline ligand **17**, Xu[28] and Norrby/Pàmies/Diéguez/Moberg[29] subsequently reported the palladium-catalyzed asymmetric allylic substitution reactions for allylic acetate **18** to afford corresponding products **19** and **20** (Scheme 6C, 6D). Guo also accomplished the allylic silyletherification of allylic carbonate **21** that converts the racemic substrate to enantiomers in the presence of chiral biquinoline catalyst $(DHQD)_2PYR$, providing silylated allylic alcohol **22** (Scheme 6E).[30]

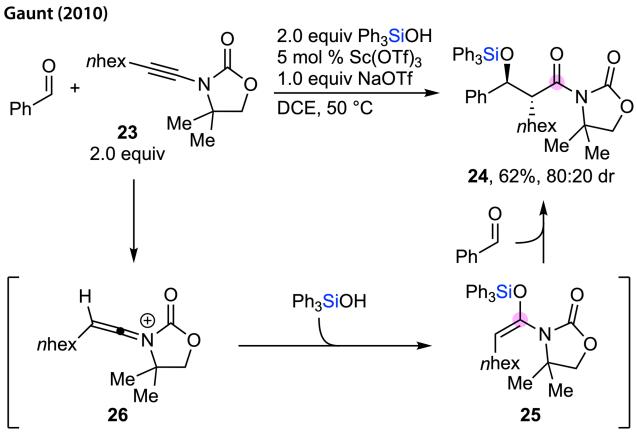
Scheme 6. Catalytic Allylic Etherification of Allylic Electrophiles with Silicon Nucleophiles.



In 2010, Gaunt reported the reaction of ynamides with silanols for the synthesis of intermediate silylenolates (enol-aminals) in the presence of a Lewis acid catalyst, followed by a Mukaiyama-type aldol reaction with aldehydes (Scheme 7).[31] For example, treatment of ynamide **23** with benzaldehyde affords the aldol product **24** with good *anti*-selectivity. The key silylenolate

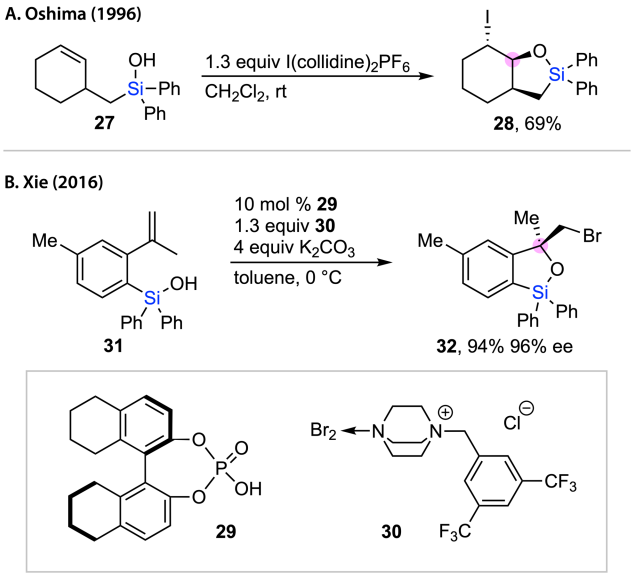
intermediate **25** is obtained through the attack of triphenylsilanol on the keteniminium intermediate **26**. In this reaction, the choice of silanol nucleophile type directly affects the *syn/anti*-selectivity of the silanol addition.

Scheme 7. Stereoselective *Anti*-selective Aldol Reaction of Ynamide with Benzaldehyde via Silylenolate Intermediate.



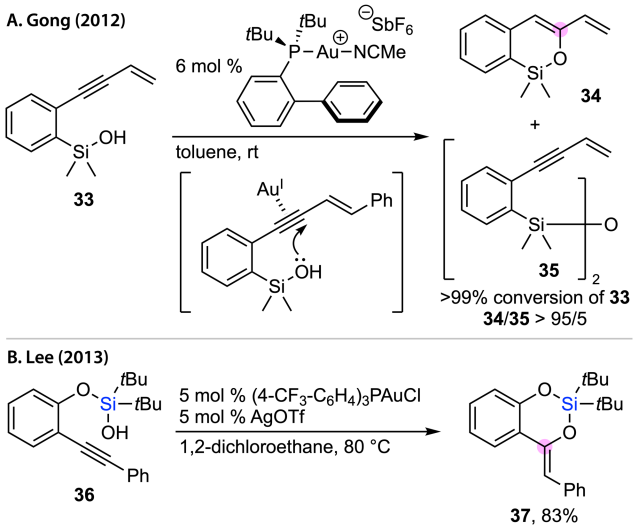
The high ability of nucleophilic silanols is reflected in the development of various cyclization reactions. The starting point for these reactions is the intramolecular iodoetherification of silanols developed by Oshima (Scheme 8A).[32] Silanol that bears an alkenyl moiety **27** is converted into the cyclized product **28** in good yield. Asymmetric intramolecular bromoetherification using a combination of chiral phosphoric acid catalyst **29** and a brominating agent **30** was also reported by Xie (Scheme 8B).[33] The 5-*exo-trig* cyclization of silanol **31** affords the chiral bromoetherification product **32** in excellent yield.

Scheme 8. Pioneering Intramolecular Haloetherification of Silanols.



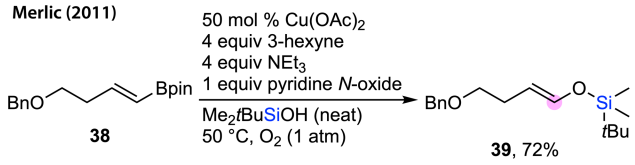
An example of an intramolecular reaction of silanol species is the 6-*endo-dig* cyclization reported by Gong using Au(MeCN)SbF_6 with JohnPhos as a catalyst for the activation of the triple bond (Scheme 9A).[34] Under these optimized conditions, silanol **33** is fully consumed to afford oxasiline **34** with much reduced formation of siloxane **35**. The cationic gold catalyst is supposed to activate the triple bond to promote the intramolecular addition of the hydroxysilyl group. The similar Au-catalyzed 6-*endo-dig* cyclization of silanol moiety was also reported.[35] Lee subsequently reported on analogous intramolecular 6-*exo-dig* cyclization reactions of silanol **36** using a gold catalyst to furnish cyclized product **37** (Scheme 9B).[36]

Scheme 9. Au-catalyzed Intramolecular Hydrosiloxylation of Silanol.



Merlic reported the Cu-catalyzed Chan–Lam-type oxidative coupling of alkenylboronate **38** to afford terminal silyl enol ether **39** with stereoretention, demonstrating silanolate species as a coupling partner in copper-catalyzed coupling reactions (Scheme 10).[37] This reaction could furnish silyl enol ethers that are generally challenging to synthesize from the corresponding aldehydes.

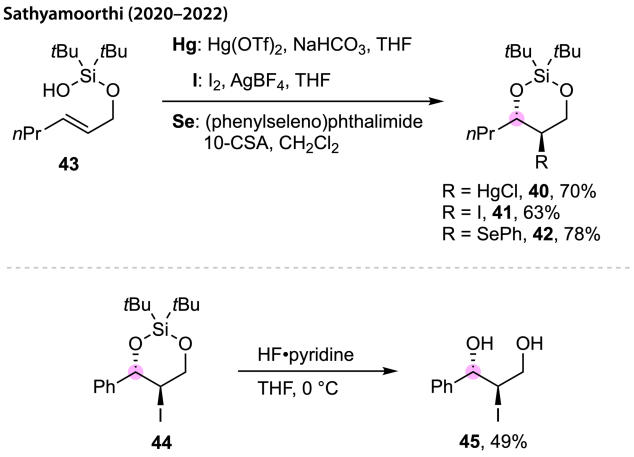
Scheme 10. Cu-catalyzed Oxidative Synthesis of Silyl Enol Ether from Alkenylboronate.



These seminal works form the basis for catalytic transformations in which compounds with siloxy moieties can be constructed. Sathyamoorthi reported intramolecular reactions using tethered silanols, to applications in intramolecular oxymercuration, iodoetheration, and oxyselenation (Scheme 11).[38] Cyclized products **40**, **41**, and **42** can be obtained from tethered silanol **43** through

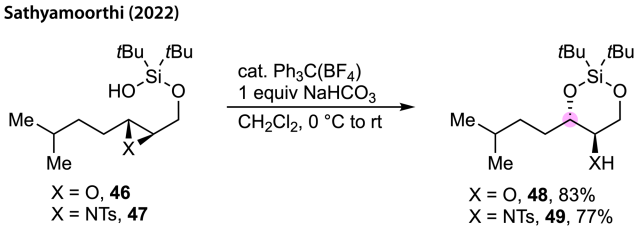
the activation of the alkene moiety and subsequent cyclization. The removal of the silicon linker from the iodosiloxylated product **44** is also facile, affording 1,3-diol **45**.

Scheme 11. Intramolecular Oxymercuration, Iodoetheration, and Oxyselenation of Tethered Silanol.



Recently, they have reported a catalytic method for the synthesis of six-membered cyclic silyl diethers by regioselective ring-opening of aziridines and epoxides (Scheme 12).[39] The ring-opening reactions of epoxide **46** and aziridine **47** can be performed under catalytic activation conditions using trityl cation to deliver cyclized products **48** and **49**, respectively. The application of tethered silanols suggests the possibility of introducing a variety of oxygen functional groups to organic molecules.

Scheme 12. Ring Opening of Epoxide and Aziridine by Tethered Silanols.

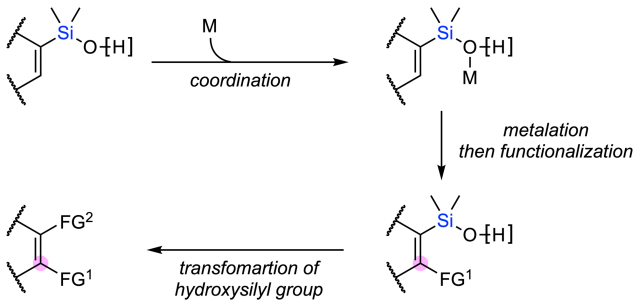


The reactions mentioned above demonstrate that silanols function as a highly nucleophilic and sizable water surrogate. Due to the differences between silanols and water in terms of acidity and steric bulkiness, silanols enable the delivery of oxygen functional groups with unique selectivity.

3. Silanols as Temporary Ligands to Control Regioselectivity of Metal-Catalyzed Reactions

Silanols/silanolates are known to have the ability to direct metals into proximal positions through coordination to the metal center, similar to carboxylic acids and amides (Scheme 13). This coordination effect of a hydroxysilyl group on metals enables the regioselective metalation that can be used for the regioselective functionalization. Hydroxysilyl groups can also be removed by the treatment with fluoride anions or transformed via transmetalation for coupling reactions with other functional groups, which will be further reviewed in the next section. These features of organosilanols have garnered widespread attention in the synthetic fields for the application of hydroxysilyl groups as transformable directing groups.

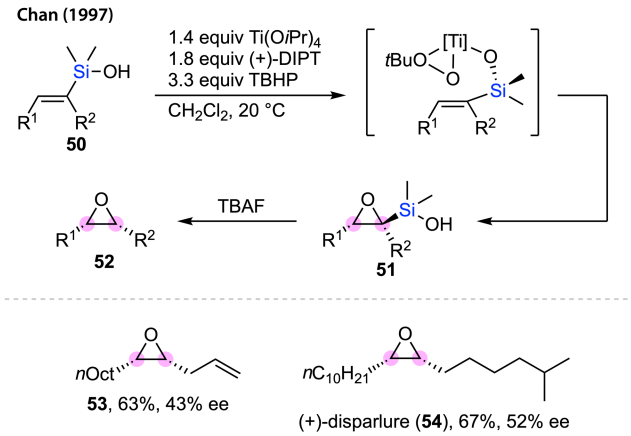
Scheme 13. Hydroxysilyl Groups as Directing Groups for Metal Centers.



One representative example is the application of enantioselective Sharpless epoxidation reactions to alkenylsilanols instead of allylic alcohols that has been investigated since the first report by Chan.[40] They found that a variety of alkenylsilanols **50** were applicable to Sharpless-type epoxidation to afford the corresponding epoxides substituted with hydroxysilyl groups **51** (Scheme 14).[41] Treatment of the epoxides **51** with TBAF provides desilylated epoxides **52** in good yields albeit with moderate enantioselectivity. This result corroborates the hydroxysilyl group as a

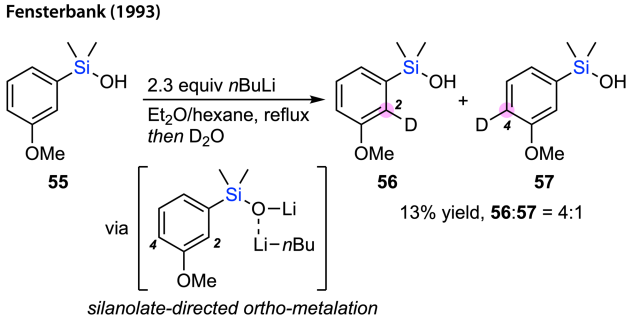
removable directing group for the titanium catalyst. This epoxidation method enabled the asymmetric synthesis of *cis*-disubstituted epoxide **53**, and the insect pheromone (+)-disparlure (**54**).

Scheme 14. Application of Sharpless-type Epoxidation to Alkenylsilanols.



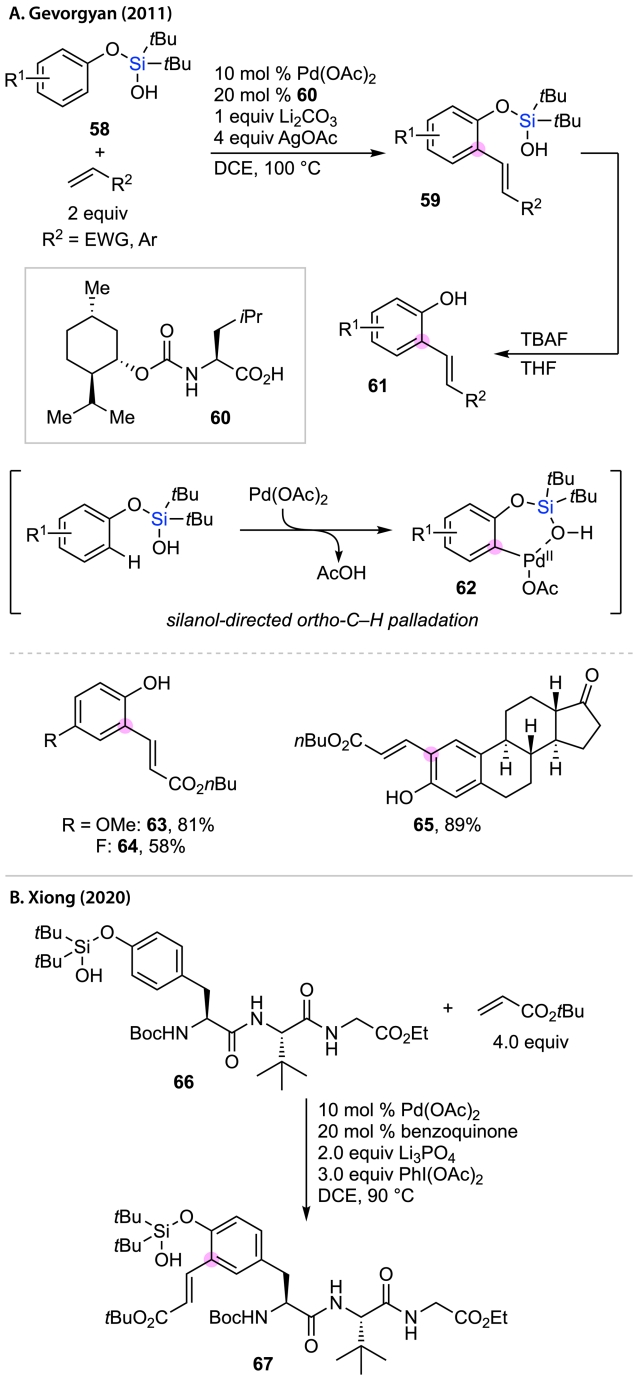
Hydroxysilyl groups are extensively examined as directing groups for *ortho*-selective C–H metalation of arylsilanols. The first report of silanol-directed C–H metalation was reported by Sieburth in 1993 (Scheme 15).[42] Lithiation of arylsilanol **55** followed by quenching with D_2O afforded products **56** and **57** as a 4:1 mixture of regioisomers. This result demonstrates that lithiation of arylsilanol **55** favors the 2-position over the 4-position, indicating the contribution of the coordination of silanolate to lithium cation.

Scheme 15. Silanol-directed C–H Lithiation of Arylsilanol.



Recently, palladium-catalyzed *ortho*-C–H functionalization of silanols has been widely investigated. Gevorgyan reported that palladium-catalyzed *ortho*-C–H alkenylation of phenol-derived silanols **58** yields alkenylated products **59** by using leucine derivative **60** as a ligand (Scheme 16A).[43] The hydroxysilyl groups of silanols **59** are easily removed by TBAF to yield the alkenylated phenols **61**. C–H Palladation proceeds solely at the *ortho*-position due to the coordinating effect of the silanol moiety to the palladium center to afford the *ortho*-metalated **62** as the key intermediate. Electron-donating and neutral phenols and electron-deficient alkenes, including styrene derivatives, were amenable to these transformations. This reaction provides moderate to good quantities of the desired products **63** and **64**. It is noteworthy that the palladium-catalyzed C–H alkenylation of *meta*-substituted phenols proceeds to afford alkenylated products selectively at the less hindered *ortho*-position. Mono-alkenylated estrone **65** was obtained in excellent yield from the corresponding silanol. Xiong extended this C–H alkenylation strategy to silanol **66**, derived from the phenolic moieties of tyrosine residues in peptides, to give rise to alkenylated product **67** to demonstrate the high functional group compatibility of the reaction (Scheme 16B).[44]

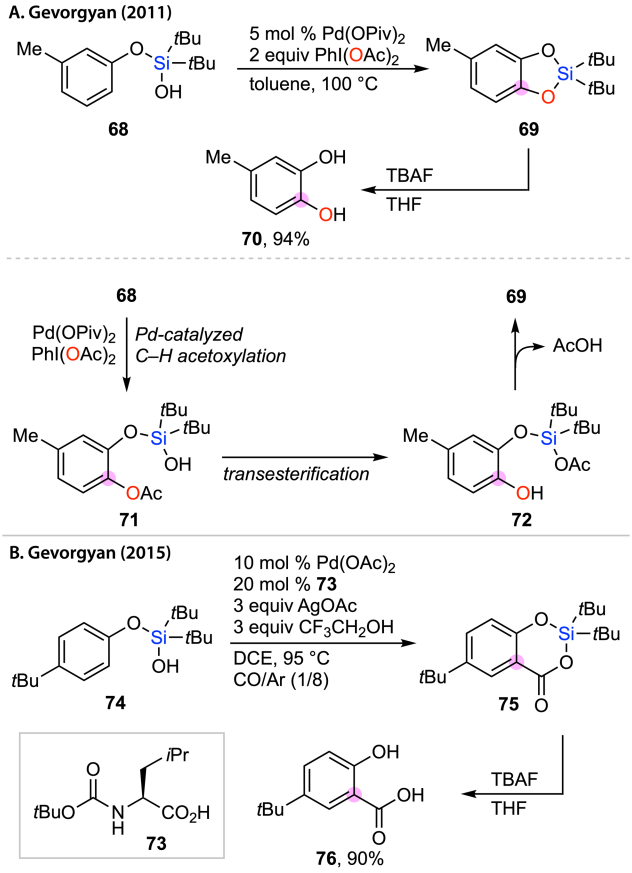
Scheme 16. Pd-catalyzed *Ortho*-C–H Alkenylation of Phenol-derived Silanols.



Treatment of silanol **68** with $PhI(OAc)_2$ in the presence of a catalytic amount of $Pd(OPiv)_2$ affords silacyclic product **69** (Scheme 17A).[45] Further desilylation of **62** with TBAF produces catechol derivative **70** in excellent yield. The proposed reaction mechanism involves the silanol-directed

palladium-catalyzed *ortho*-C–H acetoxylation of **68**, which generates acetoxylated arene **71**. Subsequent transesterification of silanol **71** affords arene **72**, which subsequently undergoes cyclization to afford **69**. This transesterification step was supported by the complete loss of the ^{18}O-atom in the product **69**, which had been installed as the silanol ^{18}OH moiety of labeled **68**. Palladium catalyst ligated with leucine derivate **73** enables carbonylation of phenol-derived silanol **74** through silanol coordination, resulting in the formation of silacycle **75**, which is then converted into the salicylic acid derivative **76** in high yield upon treatment with TBAF (Scheme 17B).[46] The formation of silacycle **75** is believed to occur through the initial formation of an *ortho*-metalated intermediate such as **62**, followed by CO insertion and subsequent reductive elimination.

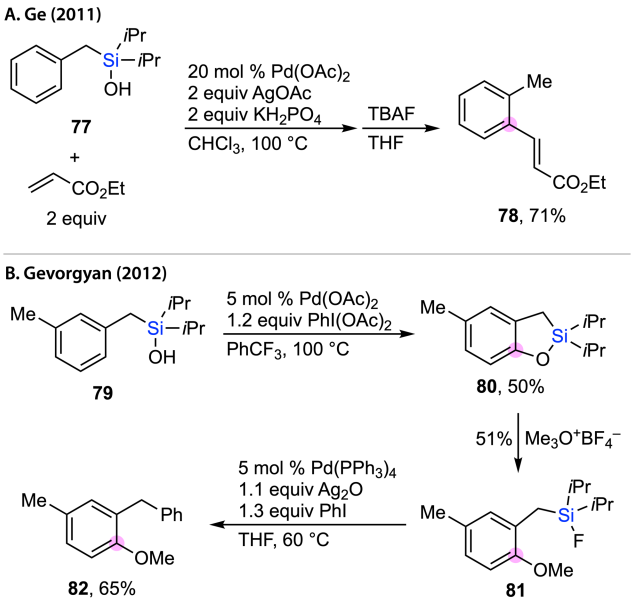
Scheme 17. Pd-catalyzed *Ortho*-C–H Hydroxylation and Carbonylation of Phenols Directed by Silanols.



Similarly, benzylsilanol **77** has also been shown to be applicable to silanol-directed, *ortho*-C–H alkenylation, followed by the removal of the silanol moiety to furnish the *ortho*-functionalized toluene derivative **78** in good yield (Scheme 18A).[47] Palladium-catalyzed oxygenation enables the transformation of benzylsilanol **79** into oxasilacycle **80** in moderate yield (Scheme 18B).[48] The reaction of silacycle **80** with Meerwein salt ($Me_3O^+BF_4^-$) produces fluorinated silane **81**. The palladium-catalyzed cross-coupling reaction of **81** with iodobenzene affords the coupled product **82**. These results highlight the dual role of silanol moieties as both directing groups and transformable functional groups. Similary to the use of phenol-derived silanols shown in Scheme

16 and 17, the coordination of the silanol moieties of benzylsilanols in Scheme 18 is supposed to be responsible for the *ortho*-selective C–H palladation.

Scheme 18. Pd-catalyzed *Ortho*-C–H Functionalization of Benzylsilanols.



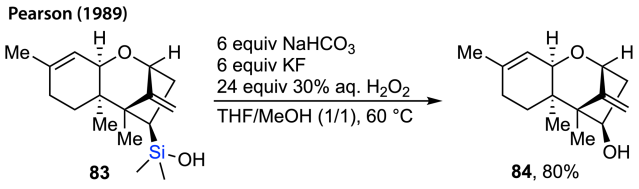
The series of reactions mentioned above demonstrate the unique value of the hydroxysilyl groups of silanols as directing groups for metal atoms. By taking advantage of their easily removable and transformable properties, silanol moieties allow the synthesis of functionalized compounds that are difficult to obtain with other directing groups.

4. Silanols as Coupling Partners for Transferring Functional Groups

Hydroxysilyl groups can serve as transformable functional groups. Among the compounds with those functional groups, such as boronic acids/esters or stannanes of widespread utility,[49] silanols are known to have much less toxicity problems. Consequently, leveraging silanol and silanolate moieties in organic synthesis has become a hot research area.[2f]

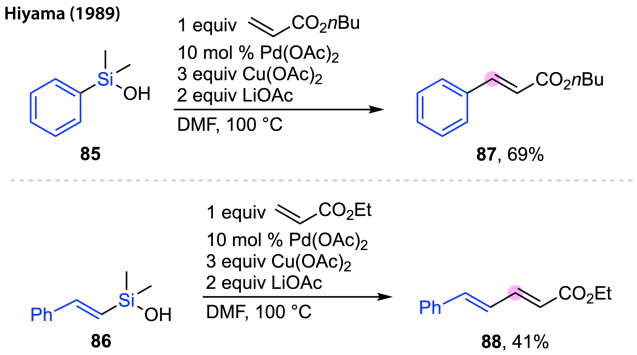
One of the most well-known transformations of the silyl group is the Tamao–Fleming oxidation that converts an activated silyl group into a hydroxy group.[50] Albeit less commonly employed, a hydroxysilyl group can also be directly transformed into a hydroxy group under Tamao oxidation conditions (Scheme 19).[51] This particular transformation of silanols has been discovered in Pearson's total synthesis of trichodermol, which demonstrated the conversion of the complex intermediate **83** to the corresponding alcohol **84**.

Scheme 19. Tamao Oxidation of the Hydroxysilyl Group.



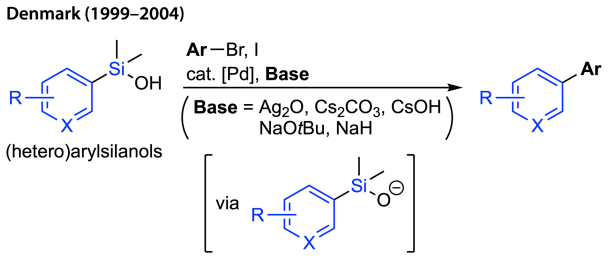
The first example of the transformation of hydroxysilyl groups into carbon substituents is the oxidative Mizoroki-Heck-type reaction of alkenes using aryl- and alkenylsilanols such as **85** and **86** reported by Hiyama in 1998 (Scheme 20).[52] This transformation yielded arylated and alkenylated products **87** and **88** in moderate to good yields, indicating that silanols can function as arylating and alkenylating reagents in transition-metal-catalyzed coupling reactions.

Scheme 20. First Report of Harnessing Silanols as Reagents for Transferring Carbon Substituents.



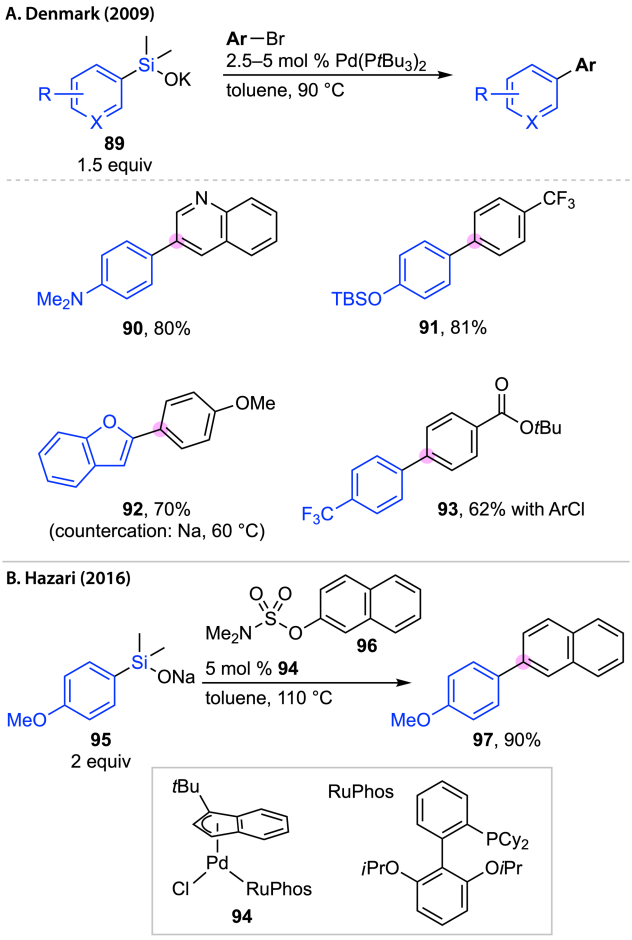
Among such coupling reaction using silanols, arylation reaction that employs arylsilanols has received the most attention. Since the initial report by Hiyama, numerous studies have reported on palladium-catalyzed arylation reactions of (hetero)arylsilanols with aryl bromides or iodides in the presence of various bases (Scheme 21).[53] The proposed mechanism involves the in situ generation of (hetero)arylsilanolates through deprotonation of the corresponding silanols, which is highly nucleophilic as seen in Chapter 2 and serve as a potent ligand to the center of the metal catalyst. Collectively, these species serve as key intermediates in these reaction systems.

Scheme 21. Pd-catalyzed Arylation Reactions with Arylsilanols as Arylating Reagents.



In these contexts, Denmark discovered that these metal (hetero)arylsilanolate salts can be obtained as mostly solid reagents that are useful in palladium-catalyzed cross-coupling reactions.[54] These silanolates can be stored at room temperature in a dry environment, and their use obviates the need for external bases and prevents the formation of disiloxanes through intermolecular condensation. Denmark reported palladium-catalyzed arylation of aryl bromides with potassium (hetero)arylsilanolates **89** bearing various substitutions on the aryl rings (Scheme 22A).[54d] The reaction allows a broad range of electronic and steric scope for both aryl bromides and potassium arylsilanolates. Thus, the coupling reactions of the preformed potassium arylsilanolates with aryl bromides provides biaryls **90** and **91** in good yields. Certain potassium heteroarylsilanolate, 2-benzofuryl, was found to decompose during synthesis. The instability of such a potassium salt was resolved by using the corresponding sodium salts. The sodium silanolate bearing 2-benzofuryl group can be prepared as a stable solid and was reported to transfer the corresponding aryl group to afford biaryl **92** in good yield. Besides, aryl chlorides also work well as substrates in this reaction system, resulting in good yields of biaryl **93**. Hazari also demonstrated that in the presence of palladium catalyst **94**, sodium arylsilanolates **95** is applicable to arylation of aryl sulfamate **96** via C–O bond cleavage to furnish biaryl **97** in good yield (Scheme 22B).[55] These results establish arylsilanolates as versatile arylating reagents.

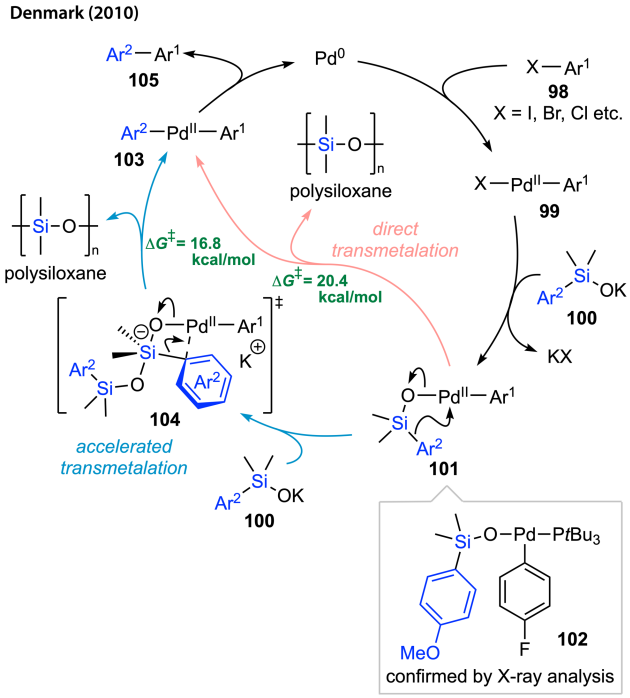
Scheme 22. Pd-catalyzed Arylation Reactions of Aryl Halides with (hetero)Arylsilanolates.



Denmark postulated a plausible reaction mechanism for the palladium-catalyzed arylation of aryl halides with potassium arylsilanolates (Scheme 23). The oxidative addition of aryl halide **98** to Pd(0) species produces arylpalladium(II) intermediate **99**. Anionic arylsilanolate **100** attacks to intermediate **99** to furnish arylpalladium(II) intermediate **101** with a loss of the potassium salt. The X-ray structure of the dimethyl(4-methoxyphenyl)silanolate-coordinated arylpalladium(II) ligated with tri-*tert*-butylphosphine **102** was obtained,[56] supporting the in situ formation of silanolate-coordinated palladium species such as **101**. Two mechanistic pathways have been proposed for the generation of palladium intermediate **103** via the intramolecular transfer of the aryl group to the

palladium center.[57] One is the direct transmetalation pathway (depicted in red) where the aryl group is directly transferred to the palladium center, which proceeds from silanolate-coordinated intermediate **101**. The other is the accelerated transmetalation pathway (depicted in blue), where an external silanolate is involved in the transfer of the aryl group via a silicate transition state **104** thereby promoting the transfer process. In both pathways, the generation of palladium intermediate **103** and polysiloxane byproduct occurs, followed by reductive elimination to form biaryl compound **105** and regenerate active Pd(0) species. Kinetic analysis by the same group elucidated that the migration pathway assisted by an external silanolate (blue arrow) is much faster than the non-assisted migration from neutral palladium(II) intermediate **101** (red arrow). This study suggests that an external silanolate promotes the migratory pathway in the catalytic reaction system. Furthermore, DFT calculations show that the activation barrier for the transfer of the aryl group via transition state **104** (16.8 kcal/mol) is lower than that from neutral arylpalladium(II) intermediate **101** (20.4 kcal/mol), which is consistent with the kinetic studies.

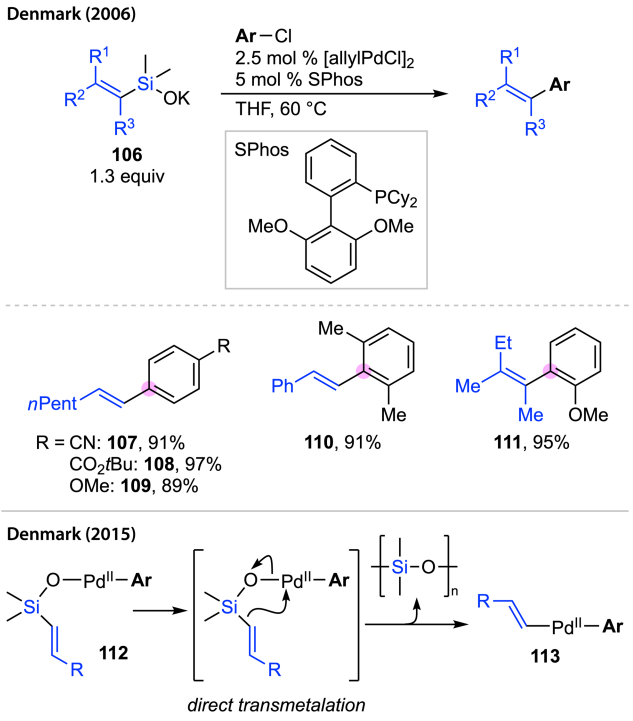
Scheme 23. Plausible Reaction Mechanism for Pd-catalyzed Cross-coupling Reactions of Aryl Halide with Potassium Arylsilanolate.



Silanols are reported to have the ability to transfer carbon substituents other than aryl groups. For example, as in the case of arylsilanolates, potassium alkenylsilanolates **106** can also be prepared and are applicable to palladium-catalyzed alkenylation of aryl chlorides (Scheme 24).[58] Aryl chlorides bearing electron-donating and -withdrawing groups were tolerated (**107**–**109**). *Ortho*-disubstituted arene were converted into alkenylated arene **110** in excellent yield. Alkenylsilanolates allow the transfer of alkenyl groups of various substitution patterns without loss of stereochemistry, which could provide even a tetrasubstituted alkene **111** as a coupled product. The mechanism behind the migratory step of the alkenyl group was also investigated through kinetic studies by a series of the amount of silanolate to propose that potassium alkenylsilanolates allow the rapid transfer of the alkenyl group from the neutral arylpalladium(II) silanolate intermediate **112** to afford alkenylpalladium(II) intermediate **113** with concomitant

formation of the waste polysiloxane.[59] Given that the migration of aryl groups is proposed to proceed via the penta-coordinate silicate transition state, the transmetalation mechanism using silanolate species appears to depend on the functional groups to be transferred.

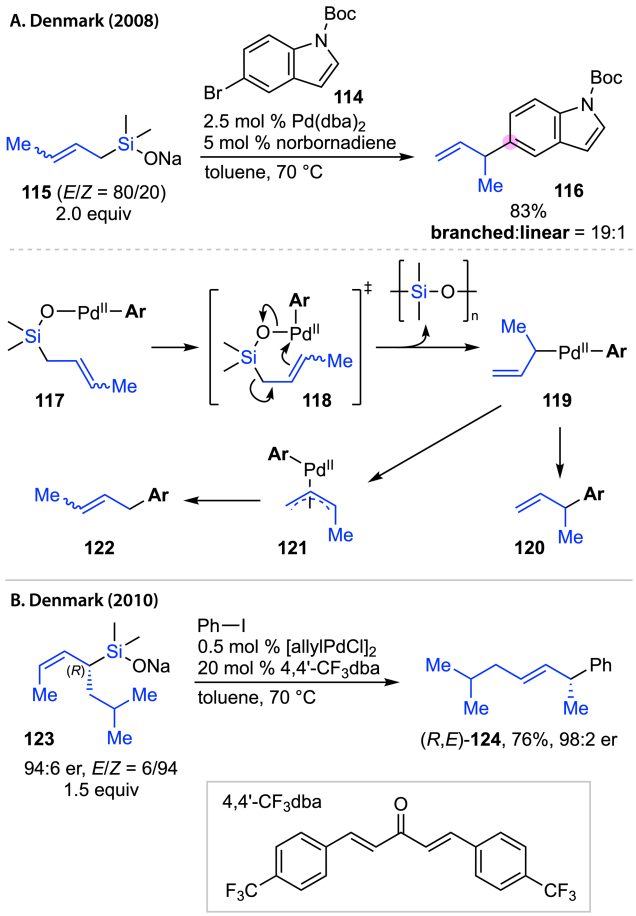
Scheme 24. Pd-catalyzed Alkenylation of Aryl Chlorides with Potassium Alkenylsilanolates.



Allylsilanolates can act as allylating reagents in the presence of a palladium catalyst.[60] The crotylation of indole **114** using 2-butenylsilanolate **115** (*E*/*Z* = 80/20) generates branched product **116** as the major product with good branched/linear selectivity (Scheme 25A). A possible mechanism accounting for the high selectivity with silanolate **115** involves the transmetalation of the crotyl group through the silanolate-coordinated arylpalladium(II) intermediate **117** via the six-membered transition state **118** to furnish σ-allyl(aryl)palladium **119**, along with the elimination of waste polysiloxane. The subsequent reductive elimination yields rise to the branched product **120**. The use of norbornadiene as a ligand is thought to facilitate reductive elimination due to its high

π-acidity, precluding σ-π isomerization via η^3-allylpalladium intermediate **121**, which provides the linear product **122**. Upon utilization of the enantioenriched α-substituted allylic silanolate **123**, branched (*R*,*E*)-product **124** is obtained in a site- and stereo-controlled manner (Scheme 25B).[61]

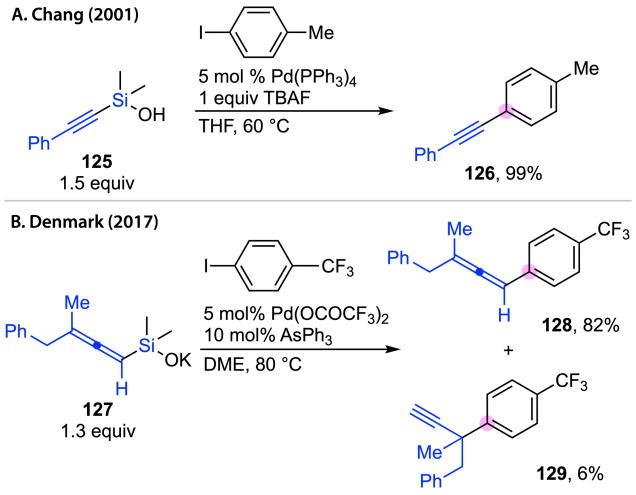
Scheme 25. Cross-coupling Reactions of Aryl Bromides with Allylic Silanolates.



Chang reported that the palladium-catalyzed alkynylation of 4-iodotoluene with alkynylsilanol **125** and TBAF as an activator results in the formation of the alkynylated product **126** in high yield (Scheme 26A).[62] Later, a similar transformation using potassium trimethylsilanolate as an activator and copper iodide as a co-catalyst was reported by Denmark.[63] Additionally, Nishimura/Hayashi reported on the feasibility of conjugate alkynylation reactions using alkynylsilanols.[64] These

findings demonstrate the potential of silanols as effective alkynylating reagents. Moreover, using allenylsilanolate **127** proved beneficial in transferring the allenyl group to produce arylallene **128** in high yield, with minimal propargylarene **129** formation (Scheme 26B).[65]

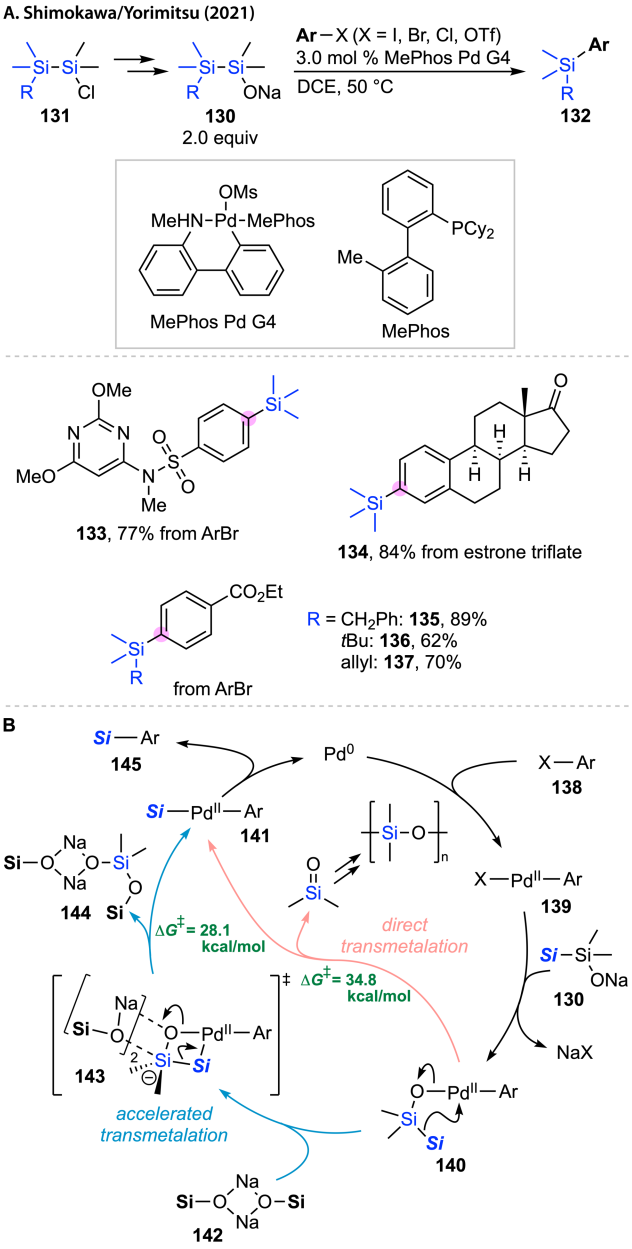
Scheme 26. Pd-catalyzed Alkynylation and Allenylation of Aryl Iodides.



Until recently, there have been no reports to use silanols/silanolates to transfer substituents other than carbon-based ones. However, considering the versatile nature of silanolate units in transferring a diverse range of carbon functional groups, it is reasonable to explore the feasibility of employing synthetic units comprising elements beyond carbon for catalytic coupling reactions mediated by transition metal catalysts. In 2021, Shimokawa/Yorimitsu reported sodium dimethylsilylsilanolate as reagents for transferring silyl groups (Scheme 27A).[66] Dimethylsilylsilanolates **130** are synthesized from the corresponding chlorodisilane **131** through hydrolysis and deprotonation. Silylsilanolates **130** were disclosed to enable palladium-catalyzed silylation of aryl (pseudo)halides, providing silylated products **132** in excellent to good yields. The mild conditions allow for the application to complex molecules to enable the synthesis of sulfadimethoxine analog **133** in good yield from aryl bromide. The silylation of estrone derivative

bearing a triflate group successfully delivered estrone derivative **134**. Dimethylsilylsilanolates allow the transfer of each of benzyl, *tert*-butyl, and allyl-substituted silyl groups (**135**–**137**) from the substituted silylsilanolates. The proposed reaction mechanism is shown in Scheme 27B. The oxidative addition of aryl halide **138** to Pd(0) species leads to the formation of arylpalladium(II) intermediate **139**, followed by ligand exchange with silylsilanolate **130** to deliver silylsilanolate-coordinated arylpalladium(II) intermediate **140**. DFT calculations suggest that the accelerated transmetalation pathway (blue arrow) of silyl group to palladium center from arylpalladium(II) intermediate **140** is more favorable than the direct transmetalation pathway (red arrow). The direct migration of the silyl group followed by the elimination of dimethylsilanone, which is finally transformed into polysiloxane, requires a high activation barrier (34.8 kcal/mol) to furnish silylpalladium(II) intermediate **141**. The accelerated migration by a cluster of silanolates **142** was revealed to proceed via transition state **143** where a silicate-like penta-coordinate structure is formed. The activation barrier of this accelerated migration pathway (28.1 kcal/mol) is approximately 6 kcal/mol lower than that of the direct migration pathway. The subsequent dissociation of siloxane byproduct **144** leads to the formation of silylpalladium(II) intermediate **141**. Eventually, reductive elimination affords arylsilane **145** with the regeneration of active Pd(0) species.

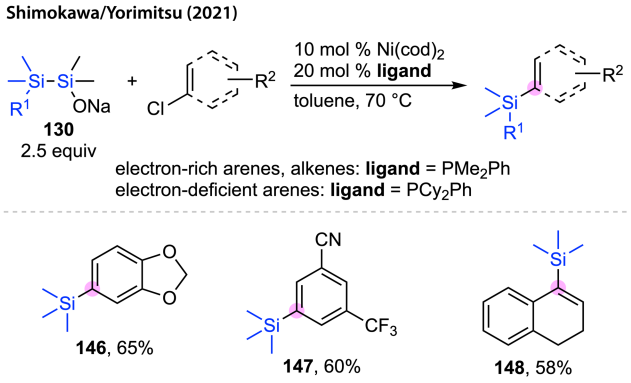
Scheme 27. Pd-catalyzed Silylation Reactions of Aryl Halides with Sodium Dimethylsilylsilanolates.



While this palladium-catalyzed silylation reaction can be applied to aryl bromides, iodides, and triflates, the silylation of less reactive aryl chlorides in combination with silylsilanolates has yet to be explored. Shimokawa/Yorimitsu therefore employed nickel-catalyzed conditions in

combination with dimethylsilylsilanolates **130** for silylation of aryl or alkenyl chlorides (Scheme 28).[67] Arylsilanes **146**, **147** are synthesized in good yields, although the use of an appropriate ligand is necessary due to the electronic nature of the substituents on the substrate molecules. This silylation reaction also affords alkenylsilane **148** from the corresponding alkenyl chloride in good yield.

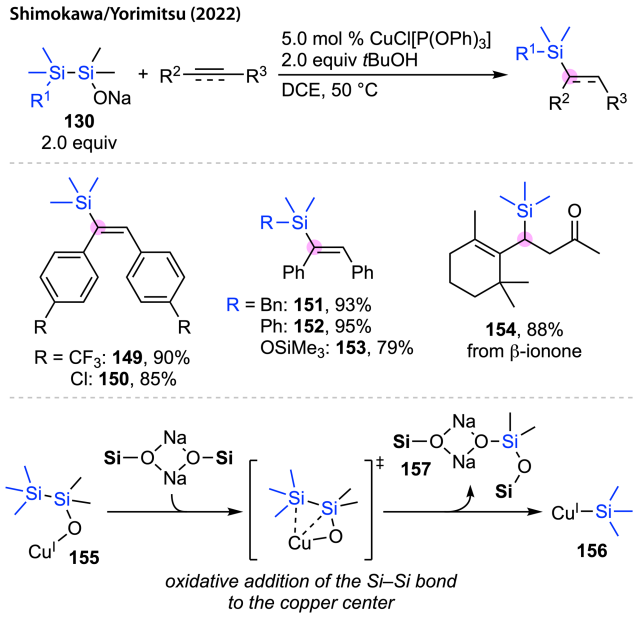
Scheme 28. Ni-catalyzed Silylation Reactions of Aryl and Alkenyl Chlorides with Sodium Dimethylsilylsilanolates.



The silylsilanolate reagent is also applicable to the generation of silylcopper species. The reactive species generated in situ could be used for copper-catalyzed hydrosilylation reactions of unsaturated bonds (Scheme 29).[68] With dimethylsilylsilanolates **130** and *tert*-butyl alcohol as a proton source, alkenylsilanes **149**, **150** were synthesized from the corresponding diarylalkynes in good yields regardless of the electronic characteristics of the substituted aryl groups. The transfer of variously substituted silyl groups gave alkenylsilanes **151**–**153** that bear benzyl, phenyl, and trimethylsiloxy groups. Alkenylsilane **153**, in particular, is a rare example of the introduction of alkoxy or siloxy-substituted silyl groups through transition-metal-catalyzed silylation. α,β-Unsaturated carbonyl compounds can also undergo conjugate addition to afford ketone **154** from β-ionone. DFT calculations suggest that the silylsilanolate-coordinated copper(I) intermediate **155**

affords silylcopper **156** via intramolecular oxidative addition of the Si–Si bond to the copper center and the subsequent loss of siloxane byproduct **157**, likely facilitated by the attack of an external silanolate dimer.

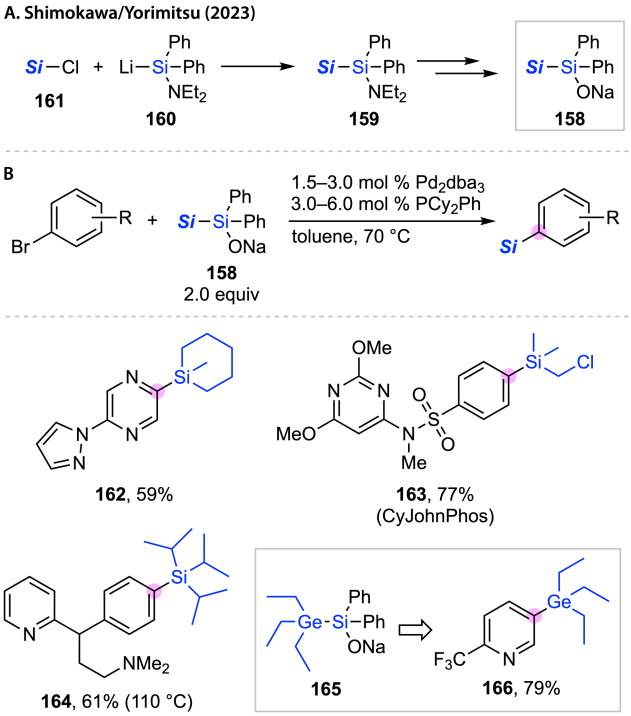
Scheme 29. Cu-catalyzed Hydrosilylation Reactions and Conjugate Addition of Unsaturated Bonds with Sodium Dimethylsilylsilanolates.



Silylation reactions using dimethylsilylsilanolates allow for fast transmetalation through the formation of a transition metal-silylsilanolate complex followed by the facile intramolecular transfer of the silyl group to the metal center, highlighting the broad applicability of these reagents for silylation reactions. However, one limitation of dimethylsilylsilanolates is the restricted scope of silyl groups that can be transferred. At least two methyl groups are required on the silyl groups to be installed because of the structural limitation arising from the restriction of starting materials. Recently, Shimokawa/Yorimitsu reported on the use of diphenylsilylsilanolates **158**, which is a modified version of silylsilanolates (Scheme 30).[69] Diphenylsilylsilanolates **158** can be synthesized from aminodisilanes **159** through hydrolysis and deprotonation in the same way as the

synthesis of **130** from **131** (Scheme 30A). A wide variety of aminodisilanes **159** can be prepared by the nucleophilic addition of silyllithium **160** to commercially available chlorosilanes **161**. This synthetic procedure therefore allows for the synthesis of diphenylsilylsilanolates that convey a broader range of silyl groups derived from chlorosilanes. The change of the procedure results in overcoming the significant limitation of the first generation dimethylsilylsilanolates that could only transfer silyl groups with at least two methyl groups. Diphenylsilylsilanolates **158** display nearly the same reactivity as dimethylsilylsilanolates in palladium-catalyzed silylation of aryl bromides (Scheme 30B). A cyclic silyl group was successfully installed into nitrogen atom-enriched substrate to afford the product **162** in moderate yield. The chloromethyl-substituted silyl group that is prone to nucleophilic substitution was also introduced to give sulfadimethoxine analog **163** in good yield. The transfer of a bulky triisopropylsilyl group is also compatible, providing arylsilane **164** in good yield, although higher temperature was required. It has also been demonstrated that a triethylgermyl group can be transferred through the corresponding sodium germyldiphenylsilanolate **165** to afford germylated pyridine **166** in acceptable yield. Germylsilanolate **165** can be synthesized by using chlorotriethylgermane in place of chlorosilanes **161**. These reactions suggest that diphenylsilanolates have the potential to transfer a variety of silyl and germyl groups irrespective of the steric and electronic properties of the silyl groups to be installed.

Scheme 30. Pd-catalyzed Silylation Reactions of Aryl Bromides with Sodium Diphenylsilylsilanolates.



The reactions discussed above strongly highlight the usefulness of silanolates as coupling partners for introducing various functional groups under mild conditions. These examples illustrate the role of silanolates as key units that function as carriers of transferrable functional groups.

Conclusion and Outlook

In this Perspective, we have reviewed the organic synthesis aspects of silanols and their broad utility, primarily in catalytic transformations. The viability of silanols is characterized by the following features: 1) synthetic utility as removable activation units of nucleophilic water surrogates, 2) the coordination ability of potentially traceless silanols that helps realize regioselective reactions, and 3) ability to form efficient donors in transition-metal-catalyzed coupling reactions. These contents are composed based on the classification of these properties. Silanols are generally regarded as difficult to handle because of the facile dehydrative intermolecular condensation to form disiloxanes. As a result, there have not been many reactions developed for silanols, even without limiting to catalytic transformations. We believe that a change in the common understanding of the ease of handling and synthesis of silanols would be of paramount importance as a step forward to further development of organic synthesis using silanols. Practical understanding is necessary for establishing the criteria under which conditions we could prevent dehydrative dimerization of certain silanols.

It would be necessary to determine the limitation of the directing group ability of silanols and silanolates from the viewpoint of the variety of applicable metal centers and detailed coordination modes based on bond distances and bond angles. It is also expected to take advantage of the fact that the silyl group itself can be easily and tracelessly converted to hydrogen or oxygen functionality. Thus, silanols have a unique synthetic appeal in that they can be utilized by leveraging both the coordinating properties of hydroxy groups as well as the transformable properties of the silicon element itself. Expansion of the application of silanol-oriented C-H functionalization to alkyl silanols would also be an important progress. For this purpose, it is necessary to expand a general synthetic method of either peripheral or skeletal alkyl silanols. The

development of new catalytic systems using silanols in the presence of transition metal catalysts has been shown to be important by the separate research from Hiyama, Denmark, and our silicon variant. While one report by Denmark details the relationship between the structure of alkenyl silanolates and the efficiency of the transfer,[70] further investigation is still needed for a more comprehensive understanding. Further structural development of silanolates toward the introduction of unprecedented functionalities, including carbon, silicon, and germanium functional groups, is expected. Development is also expected for radical reactions using silanols as substrates. Recently, MacMillan reported studies of siloxysilyl radicals based on intramolecular transfer of TMS group using tristrimethylsilylsilanol.[71] Further methodical development is envisioned for the generation of carbon and silicon radicals using various siloxy radicals as precursors. We hope that silanol chemistry will garner more and more interest through this Perspective and that silanol-related reactions will further advance.

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Notes

The authors declare no competing financial interest.

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