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Direct silylation reactions of inert C–H bonds via transition metal catalysis

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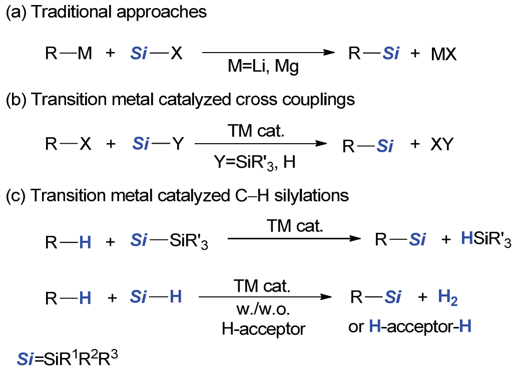
In the past thirty years, transition metal catalyzed silylation of inert C–H bonds has attracted intensive attention due to the importance and wide use of organosilicon compounds. In this review, the silylation reactions of inert C–H bonds catalyzed by transition metal complexes of Ir, Rh, Ru, Pt, Pd, Ni, and Sc, and the strategies utilized to access the site-selective C–H silylation products have been summarized. Furthermore, the mechanisms of C–H silylation reactions have been discussed briefly.

transition metal, inert C–H bond, catalysis, silylation, regioselectivity

1 Introduction

The direct C–H bond functionalization catalyzed by transition metals has attracted intensive attention in the past several decades, which provides a straightforward solution for organic synthesis starting from simple inactivated feedstocks with high atom- and step-efficiency. Among them, the direct silylation of inert C–H bonds presents a prominent example offering an easy approach to organosilicon compounds, which find wide applications in organic synthesis [1], organic materials [2], bioactive compounds [3], and so on [4]. Therefore, lots of efforts have been made in the formation of C–Si bonds of organosilicon compounds.

Traditionally, the synthetic methods for the introduction of silyl groups to organic molecules involve reactions of organolithium or -magnesium reagents with silicon electrophiles (Scheme 1(a)). In these events, the tolerance of sensitive functional groups are generally not satisfied and therefore protecting groups are often necessary in the preparation and reaction processes of these strongly nucleophilic and basic reagents. To circumvent this issue, transition metal catalyzed cross coupling reactions of aryl halides with silylative reagents such as disilanes and hydrosilanes have been developed successfully, which avoids the use of strong carbon nucleophiles (Scheme 1(b)). In principle, the direct functionalization/silylation of inert C–H bonds, ubiquitous in organic molecules, via transition metal catalysis is one of the most efficient methods for the synthesis of organosilicon compounds since such a process potentially precludes the preactivation of substrates and increases the atom- and step-economy of the whole event (Scheme 1(c)).



Scheme 1 Methods for the synthesis of organosilicon compounds.

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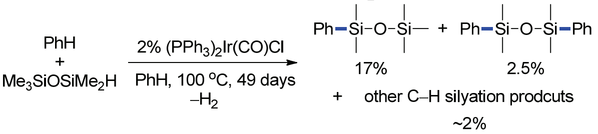
In recent years, the direct silylation reactions of C(sp^2 or sp^3)–H bonds have achieved enormous success and various transition metal complexes including Ir, Ru, Rh, Pt, Pd, Ni, and Sc have been utilized as efficient catalysts in the C–H silylation reactions (*vide infra*). The related mechanistic studies have greatly improved our understandings on how to cleave and then silylate the inert C–H bonds under mild reaction conditions with the tool of transition metal catalysis. Meanwhile, the issue of regioselectivity in C–H silylation reactions deserves more attention. There are two major strategies to control the regioselectivity in direct C–H silylation reactions: (1) utilizing a directing group for the activation of adjacent C–H bonds, such as a nitrogen atom from amines, heterocycles, and amides, an oxygen atom from carbonyls and heterocycles, and hydrosilyl ether/amine groups generated *in situ* from alcohol/amines with silanes; (2) building up a crowded environment to activate the most sterically accessible C–H bonds with the use of transition metal catalysts, ligands, substrates or even the silylative reagents.

As far as we know, there have been only few literatures partially summarizing the development of C–H silylation reactions so far [5]. A comprehensive review on the profile of this field in the past three decades especially on the impressive advances in the recent ten years is highly desirable. This personal review intends to give a whole view on the development of transition-metal-catalyzed direct silylation of inert C–H bonds covering aromatic, heteroaromatic, and benzylic as well as simple aliphatic C–H bonds. Of note, the Heck-type formal C–H silylation reactions of olefins through insertion/elimination mechanism, rather than C–H activation, will not be discussed here [6].

2 Silylation reactions of C(sp^2)–H bonds

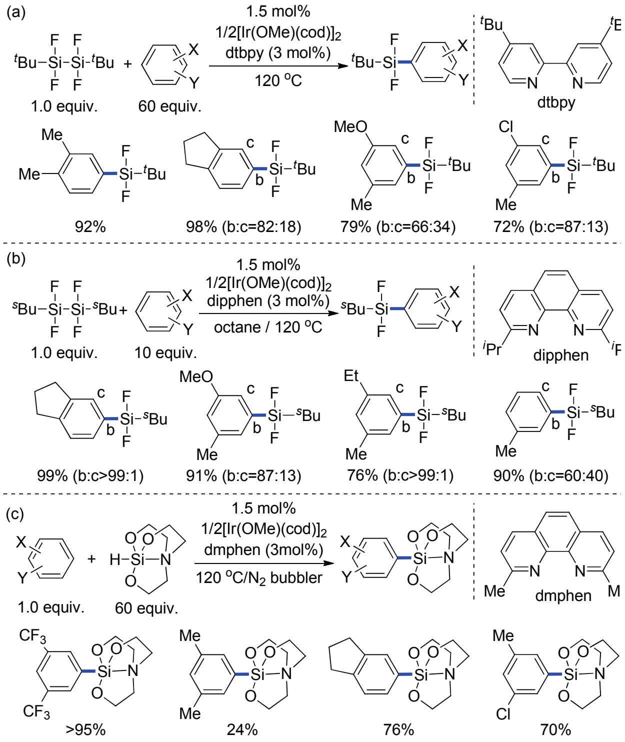
2.1 Ir-catalyzed silylation

As early as in 1982, the group of Curtis [7] first reported the Ir-catalyzed silylation of the C–H bond in benzene with hydrosilanes giving phenylsiloxanes and other redistribution products, which were monitored by GC-MS spectroscopy (Eq. (1)). Despite the low yields of the silylation products, this work opened the door for transition metal catalyzed silylation of unreactive C–H bonds. Since this seminal work, more and more attention has been paid to this area.



(1)

Twenty years later, Ishiyama *et al.* [8a] described the first synthesis of arylhalosilanes through aromatic C–H silylation under Ir-catalysis (Scheme 2(a)). However, there are two main drawbacks in this reaction: one is the limited substrate scope and low regioselectivity for substituted arenes; the other is the use of a large excess of arenes. Later on, they improved the reaction regioselectivity by using 1,2-di-*sec*-butyl-1,1,2,2-tetrafluorodisilane as a silylation source and 2,9-diisopropyl-1,10-phenanthroline as a more structurally rigid ligand (Scheme 2(b)) [8b]. Moreover, the amount of arene could be reduced to 10 equivalents with octane as an inert solvent. It should be pointed out that only half of the disilane was incorporated in the final arylsilane products. To circumvent this issue, in 2013, they developed an alternative reaction system using easily available 1-hydrosilatrane as the silylation reagent, which avoided the tedious preparation of tetrafluorodisilanes and improved the reaction economic efficiency (Scheme 2(c)) [8c].

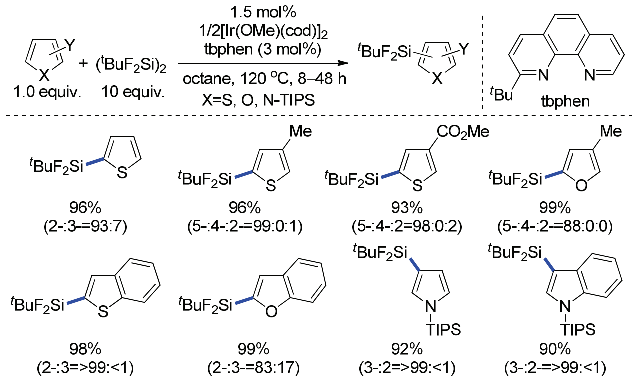


Scheme 2 Ir-catalyzed C–H silylation with fluorodisilanes and hydrosilatranes by Ishiyama and Miyaura.

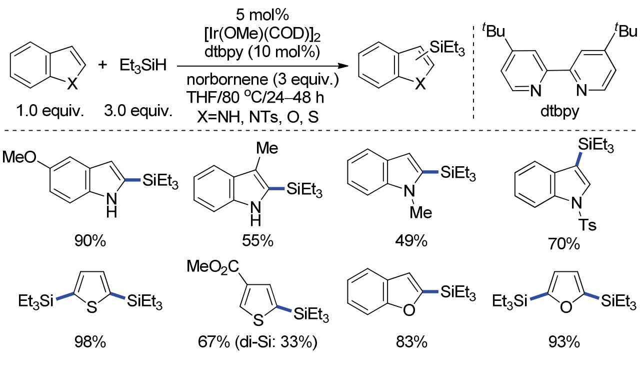
In addition, they had also extended the above methodology to the regioselective C–H silylation of five-membered heteroarenes (Scheme 3) [8d]. The regioselectivity was controlled by both electronic and steric effects. Thiophene and furan derivatives were overwhelmingly silylated at α-positions, which were more reactive than other positions due to the electronegative sulfur atom. On the other hand, β-silylated products were obtained almost exclusively for 1-triisopropysilylpyrrole and -indole because of the bulkiness of the TIPS group.

In 2008, Lu and Falck [9] described another Ir-catalyzed regioselective protocol for the C–H silylation of varied heteroarenes (Scheme 4). The presence of 2-norbornene significantly promoted the reaction efficiency. Compared with the previous work [8d], this reaction featured: (1) milder reaction conditions; (2) commercially available silylation reagents and lower excess (3 equiv.) of organosilanes; (3) complementary regioselectivity for *N*-heteroaromatic C–H silylation (except Ts-protected indole); (4) non-requirement of a protecting group on *N*-atom. The coordination between the Ir-catalyst and *N*-atom of the indole played an essential role for the observed C2 regioselectivity. Of note, bis-silylated products were sometimes obtained for *S*- and *O*-heteroarenes.

In 2010, Hartwig and coworkers [10] developed an iridium-catalyzed intramolecular *ortho*-C–H silylation of (hydrido)silyl ethers generated *in situ* from hydrosilylation of carbonyl compounds or alcohols (Scheme 5). The regioselectivity was controlled by a formally directing hydroxyl group as well as steric effects from the substrates, rather than the electronic factors. Furthermore, the addition of norbornene and 1,10-phenanthroline (phen) accelerated the reaction rate and achieved the full conversion of substrates. Two constitutional isomers were formed when a substituent, covering electron-donating and -withdrawing groups, appeared at the 3-position of the aryl ring. The ratio of the regioisomeric products was generally greater than 20:1 favoring the one silylated at the less steric hindered position, while a 1:0.79 mixture of products were obtained when the substrate bearing 3-fluoro substituent was subjected to the reaction.



Scheme 3 Ir-catalyzed C–H silylation of five-membered heteroarenes by Ishiyama and Miyaura.

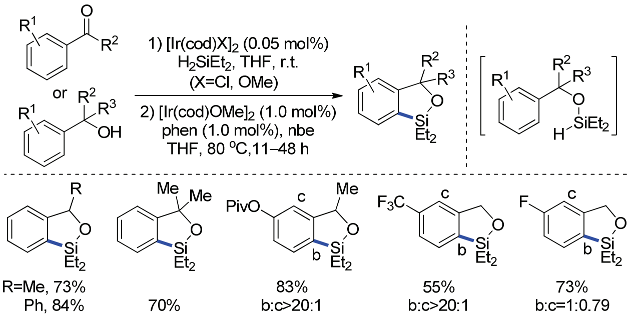


Scheme 4 Ir-catalyzed C–H silylation of heteroarenes by Lu and Falck.

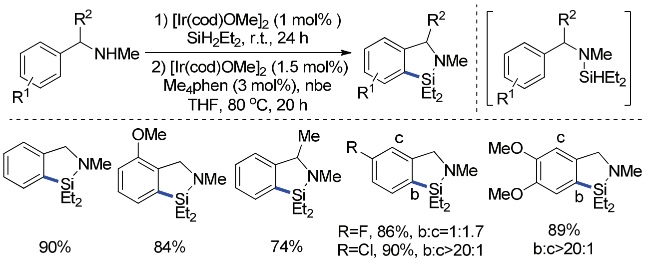
Very recently, the same group reported a similar iridium-catalyzed regioselective intramolecular silylation reaction of aromatic C–H bonds, which was directed by a second amine (Scheme 6) [11]. The C–H silylation products were amenable to the following oxidation, halogenations, and cross-coupling reactions to access diverse benzyl amine derivatives.

In 2012, Gevorgyan *et al.* [12a] developed a one-pot synthesis of dihydrobenzosiloles from styrenes and diphenylsilanes via Ni-catalyzed hydrosilylation followed by Ir-catalyzed dehydrogenative cyclization (Scheme 7). For the reactions of *meta*-substituted styrenes, the dehydrocyclization generally occurred at the less hindered positions of the aromatic rings and only single regioisomers were obtained except for the *meta*-F substituted substrate which led to a 2:1 mixture of *para*- and *ortho*-cyclized products. It should be noted that the hydrosilylation of α-substituted styrenes did not work efficiently with the above Ni-catalyst, but with the Lewis acid catalyst, B(C_6F_5)$_3$, which should be removed together with solvent before the subsequent C–H silylation step. Soon afterwards, the same group extended this strategy to the synthesis of fused heteroaromatic dihydrosiloles containing pyridine, pyrrole, furan, and thiophene rings (Scheme 8) [12b]. The functional group tolerance and regioselectivity in this reaction were also excellent.

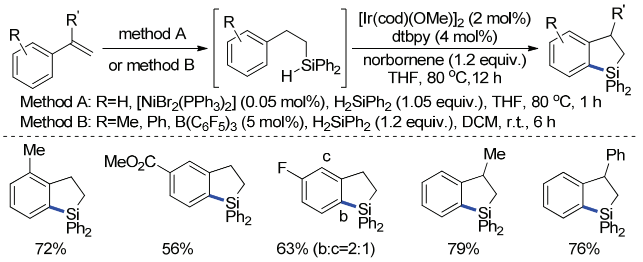
In 2013, the Mashima group [13] reported a dehydrogenative silylation reaction catalyzed by a hemilabile *N*-xylyl-*N*′-methylperimidine carbene iridium complex to give exclusively mono-*ortho*-silylation products efficiently. The proposed mechanism is shown in Scheme 9. The catalyst



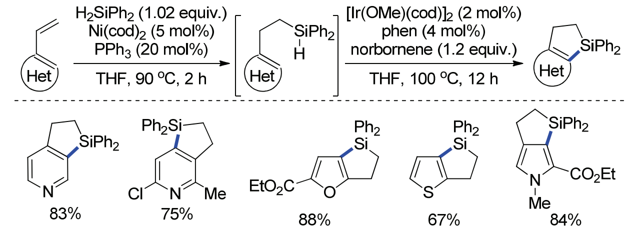
Scheme 5 Ir-catalyzed C–H silylation of aryl carbonyls and benzylic alcohols by Hartwig.



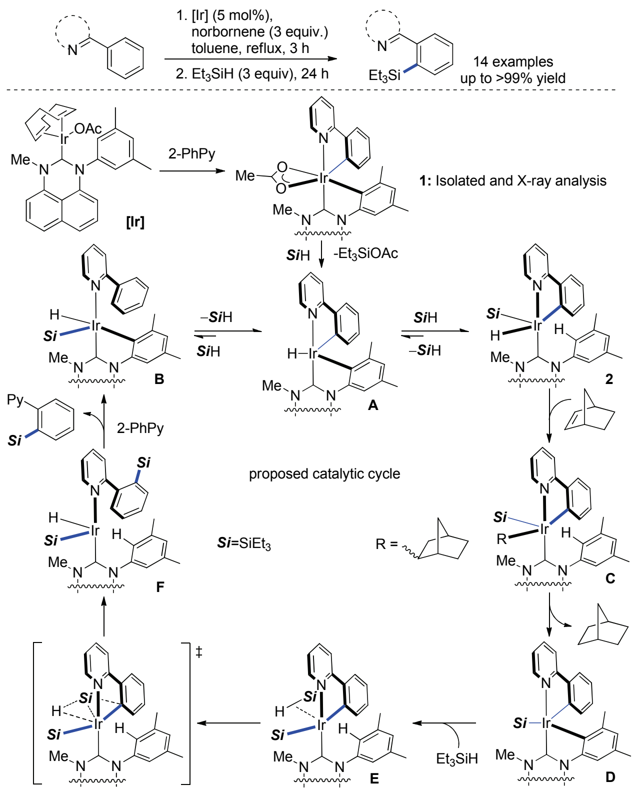
Scheme 6 Ir-catalyzed C–H silylation of benzylmethylamines by Hartwig.



Scheme 7 Hydrosilylation-dehydrocyclization reactions of styrenes by Gevorgyan.



Scheme 8 Hydrosilylation-dehydrogenative cyclization of heterocycles by Gevorgyan.



Scheme 9 Ir-catalyzed intermolecular dehydrogenative C–H silylations by Mashima.

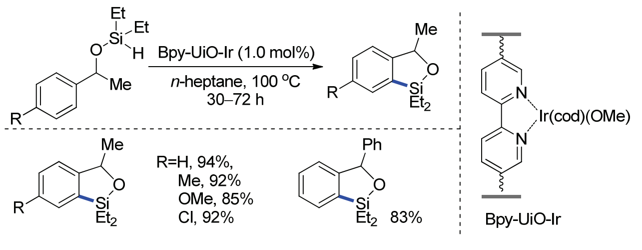
precursor **1** reacted with Et_3SiH to give a five-coordinated Ir–H species **A**. The addition of Et_3SiH to **A** resulted in the demetalation of the *N*-3,5-xylyl ring of the carbene ligand or the phenyl ring of the substrate to give **B** and complex **2**, respectively. These processes were reversible and **A**, **B** and **2** were in equilibrium. The insertion of 2-norbornene into the Ir–H bond of **2** formed species **C**. Heating the reaction mixture induced rotation and subsequent *ortho*-C(sp^2)–H bond activation of the *N*-3,5-xylyl ring of the carbene ligand affording Ir–Si species **D**. Then, the σ-bond of the Et_3Si–H coordinated to the iridium center of **D** to form species **E**. The *ortho*-silylated iridium species **F** was generated through an σ-complex-assisted metathesis (σ-CAM) intermediate. Due to the presence of the bulky $SiEt_3$ group attached to the iridium center and the *N*-3,5-xylyl group of the carbene ligand, the C–Si bond formation in this step occurred selectively.

In 2014, Lin and coworkers [14] utilized an Ir-functionalized 2,2′-bipyridyl-derived metal organic framework (MOF) of the Uio structure (Bpy-Uio-Ir) as the catalyst for the intramolecular *ortho*-C–H silylation of benzylic silylethers to obtain benzoxasiloles without any hydrogen acceptors (Scheme 10). Importantly, the Bpy-UiO-Ir catalyst was shown to be at least 1250 times more active than the homogenous control catalyst $[(CO_2Me)_2Ir(cod)(OMe)]$ because of the active site isolation in MOF, which prevented intermolecular catalyst deactivation pathways.

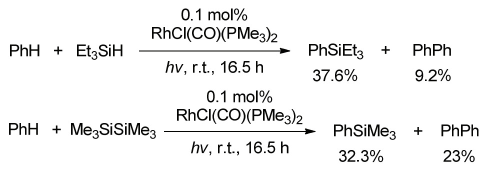
2.2 Rh-catalyzed silylation

In 1987, Tanaka *et al.* [15] described C–H silylation of benzene catalyzed by $RhCl(CO)(PMe_3)_2$ with triethylsilane or hexamethyldisilane under irradiation for 16.5 h giving triethyl- or trimethylphenylsilane in low yields (Scheme 11). The rhodium silyl species were believed to be the key reaction intermediate rather than an aryl radical or a silyl radical.

In 2008, Tobisu *et al.* [16] disclosed a Rh-catalyzed *ortho* C–H silylation reaction of 2-arylpyridines and disilanes without any hydrogen scavenger (Scheme 12). Mono- and



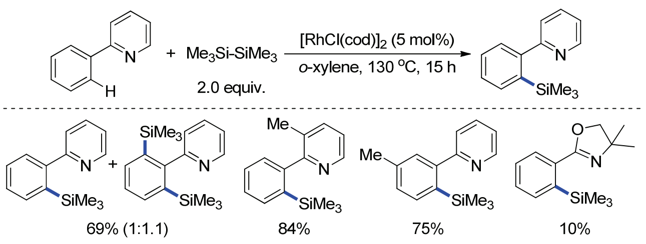
Scheme 10 Bpy-UiO-Ir catalyzed intramolecular *o*-silylation of benzylic silylethers by Lin.



$$PhH + Et_3SiH \xrightarrow[h\nu\text{, r.t., 16.5 h}]{\text{0.1 mol\% } RhCl(CO)(PMe_3)_2} \underset{37.6\%}{PhSiEt_3} + \underset{9.2\%}{PhPh}$$

$$PhH + Me_3SiSiMe_3 \xrightarrow[h\nu\text{, r.t., 16.5 h}]{\text{0.1 mol\% } RhCl(CO)(PMe_3)_2} \underset{32.3\%}{PhSiMe_3} + \underset{23\%}{PhPh}$$

Scheme 11 Rh-catalyzed C–H silylation of benzene by Tanaka.

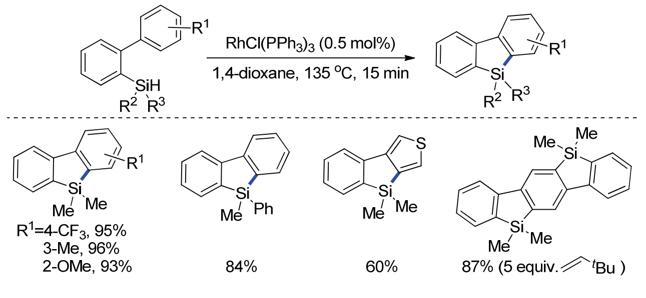


Scheme 12 Rh-catalyzed silylation of 2-arylpyridines with disilanes by Tobisu and Chatani.

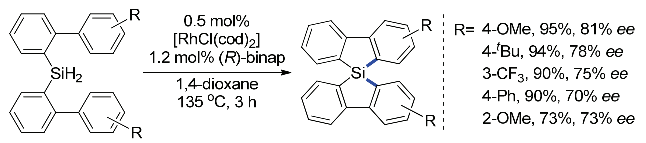
disilylated products were obtained in moderate to good yields when non-substituted pyridine was employed as a directing group. For substrates bearing bulky pyridine groups, monosilylated products could be formed with high selectivity.

In 2010, Takai and coworkers [17a] accomplished rhodium-catalyzed synthesis of silafluorene derivatives via intramolecular silylation of C–H bonds with H_2 as the only byproduct (Scheme 13). This protocol was also utilized for the synthesis of a ladder-type bis-silicon-bridged *p*-terphenyl. Later on, they extended this strategy to the asymmetric synthesis of spirosilabifluorene derivatives via twice dehyrogenative intramolecular cyclization using a Rh-catalyst with (*R*)-binap as a chiral ligand (Scheme 14) [17b].

Very recently, Hartwig's group [18a] demonstrated an elegant example of intermolecular C–H silylation of simple arenes with high *meta*-regioselectivity (Scheme 15). The reaction system contained a rhodium catalyst, a phosphine ligand, a hydrogen-acceptor, an easily available hydrosilane, and more important, an arene as the limiting reagent. This protocol featured also very mild reaction conditions (45 °C), a wide substrate scope as well as good tolerance of functional groups. The most prominent characteristic was the excellent remote steric control of the C–H silylation sites. For instance, greater than 95:5 ratio of *meta*- to *ortho*-silylated products were obtained for 1,3-disubstituted arenes. For symmetrically 1,2-disubstituted arenes, the 1,2,4-trisubstituted arylsilanes were formed with >99:1 selectivities. Indole and benzofuran derivatives underwent the C–H silylation at the 2-position with >97:3 selectivity. Silylation of 3-fluorotoluene occurred at the mutually *meta* position preferably with 89:11 selectivity. Unsymmetrically 1,2-disubstituted arenes were very challenging substrates and therefore required the use of more steric demanding ligand **L1** compared with the ligand **L2**. In general, the steric effects of the remote *meta* substituents predominated the regioselectivity of the C–H silylation sites. Meanwhile, the second-leading influence of electronic effects could render the C–H silylation occur at the more electron-rich site of arenes, which were manifested by the substrates of *N,N*-dimethyaminobenzene and trifluoromethylbenzene. The resulting arylsilanes could be transformed into a variety of useful compounds by oxidations, halogenations, cross couplings, and so on. Also, the silyl groups could tolerate a range of classical organic transformations, rendering it possible to transform the silyl groups at the late-stage of complex molecule syntheses.

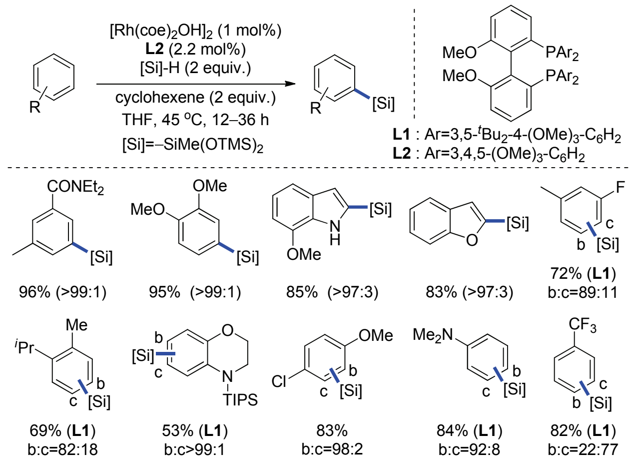


Scheme 13 Rh-catalyzed silafluorene synthesis via C–H silylation by Kazuhiko and Takai.

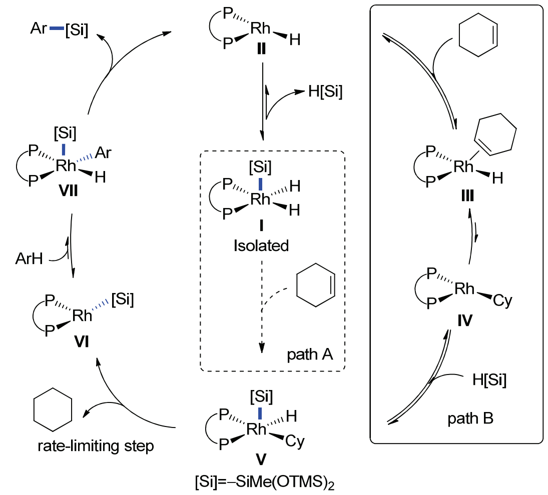


Scheme 14 Rh-catalyzed synthesis of chiral spirosilabifluorenes by Kuninobu and Takai.

Soon afterwards, the same group [18b] reported the detailed mechanistic study on the above Rh-catalyzed C–H silylation reaction based on in-depth experimental and computational observations (Scheme 16). A Rh(III) silyl dihydride phosphine complex **I** was isolated and fully characterized, which was deemed as the resting state of the catalyst. After analysis of results from kinetic experiments, stoichiometric reactions, kinetic isotope effects, and DFT calculations, the authors concluded that the silylation process of arenes initiated with the formation of Rh(I) hydride **II** generated by reductive elimination of Rh(III) complex **I** releasing a hydrosilane. Reduction of cyclohexene, the hydrogen acceptor in the reaction, by active catalytic species **II** gave intermediate **IV** via the coordination complex **III**. Oxidative addition of hydrosilane to **IV** resulted in the formation of intermediate **V** (path B). The direct hydrogen



Scheme 15 Rh-catalyzed regioselective C–H silylation of arenes by Hartwig.



Scheme 16 Proposed mechanism for the C–H silylation of arenes by Hartwig.

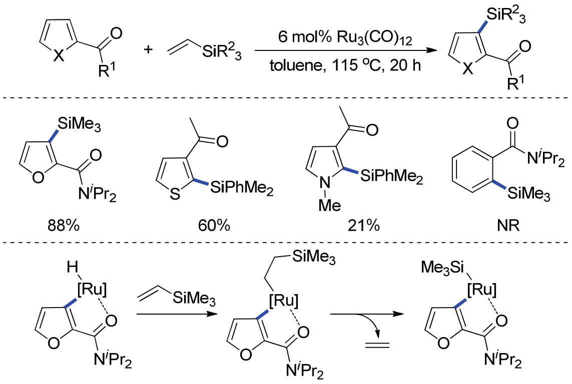
transfer from Rh(III) silyl dihydride **I** to cyclohexene generating **V** was not consistent with the experimental results (path A). Reductive elimination of **V** afforded the rhodium silyl intermediate **VI**, and this intermediate reacts with the arene to give the Rh(III)-silyl aryl hydride complex **VII**. Complex **VII** underwent reductive elimination to form the final arylsilane product. It was not the C–H oxidative addition step but the reductive elimination of cyclohexane being the rate-limiting step in the catalytic cycle. Also, the influence of arene substituents on the regioselectivity of C–H silylation and the individual steps in the catalytic cycle were discussed in detail in this work.

2.3 Ru-catalyzed silylation

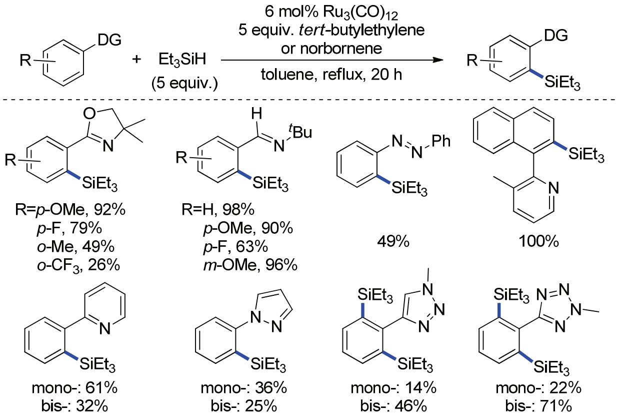
In 2000, Murai and coworkers [19a] reported $Ru_3(CO)_{12}$-catalyzed direct C–H silylation reactions of five-membered heteroarenes bearing carbonyl groups with vinylsilanes, which were utilized as silylative reagents as well as H_2 acceptors (Scheme 17). Unfortunately, this strategy was only suitable for a very limited number of heteroaromatic compounds, yet not applicable to common benzene derivatives. Oxidative addition of C–H bond gave ruthenium hydride species, which underwent olefin-insertion affording alkyl ruthenium intermediate. The following β-silyl elimination led to the key silyl ruthenium species, which accounted for the product formation through reductive elimination.

One year later, they developed a catalytic system of $Ru_3(CO)_{12}$ or $Ru(H)_2(CO)(PPh_3)_3$ for the C–H silylation of oxazoline-containing arenes with triethylsilane as a silylation reagent and *tert*-butylethylene as a hydrogen scavenger [19b]. Shortly afterwards, the same group [19c,19d] conducted a detailed study to probe into the scope, limitation, and mechanism of $Ru_3(CO)_{12}$-catalyzed silylation of aromatic C–H bonds with hydrosilanes (Scheme 18). In general, the silylation reactions of aryloxazolines, arylimines, and azobenzene gave the mono-silylation products exclusively. However, both mono- and disilylation products were obtained as a mixture when arenes containing pyridine, pyrazole, imidazole, triazole, and tetrazole as directing groups were used in the reaction.

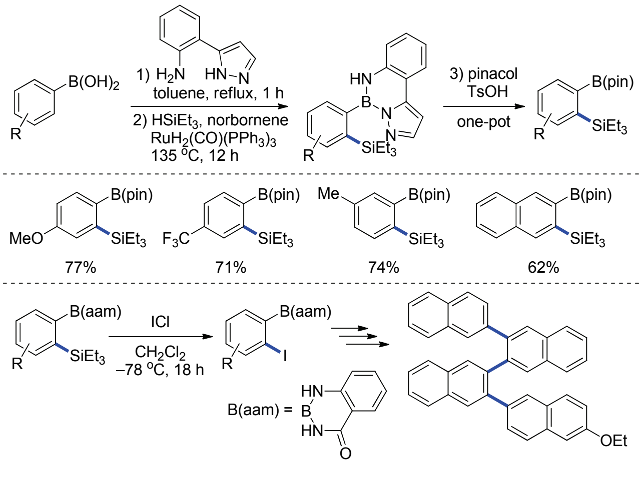
In 2009, Suginome *et al.* [20a] reported a method for the *ortho*-C–H silylation of arylboronic acids with the use of 2-pyrazol-5-ylaniline (pza) as a directing group (Scheme 19). The pza directing group was easily attached to the staring materials and detached from the products. The C–H silylation step adopted Murai's procedure as mentioned before. It was shown that the electronic effect did not matter that much to the yields of the products, but faster reaction could be observed for more electron-rich aromatic rings. Meanwhile, the fact that almost no disilylated products were detected in this reaction might attribute to the steric effect. Later on, they found anthranilamide as a better directing group with higher reactivity and stability compared with the pza group [20b]. The silyl group could be easily converted into the iodide functionality giving 2-iodoarylboronic acid derivatives, which was used as an efficient building block for the synthesis of *ortho*-linked oligoarenes via iterative Suzuki-Miyaura cross couplings [20c].



Scheme 17 Ru-catalyzed C–H silylation of heteroarenes with vinylsilanes by Murai.

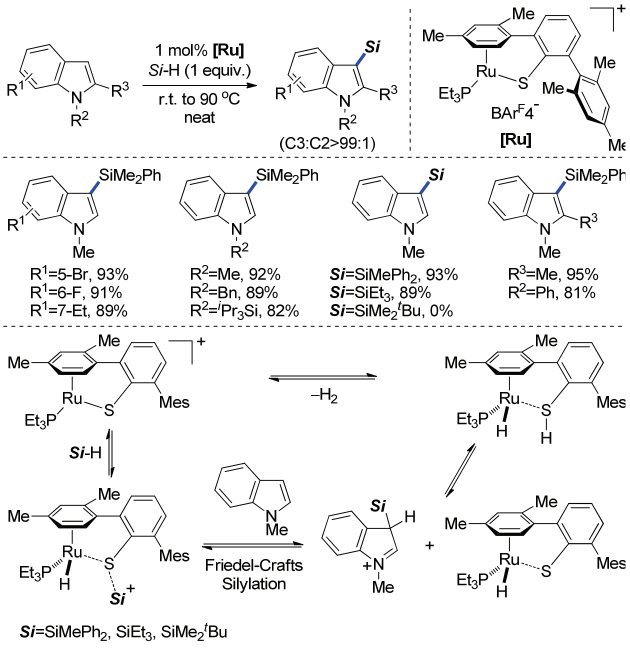


Scheme 18 Ru-catalyzed silylation of aromatic C–H bonds with triethylsilane by Murai.



Scheme 19 Ru-catalyzed C–H silylation of arylboronic acid derivatives and application to the synthesis of oligo(*o*-arene)s by Suginome.

The group of Oestreich and Tatsumi [21] collaborated to disclose a C–H silylation reaction of indoles with the use of ruthenium catalyst containing a polar Ru–S bond (Scheme 20). The reaction featured excellent C3 regioselectivity, low temperature, lack of solvent, and liberating H_2. Various substitution patterns at the indole skeleton were amenable to this reaction, for some cases with slightly higher temperature. The regioselectivity was controlled by the electronic effect; however, very steric demanding silanes such as ^{t}BuMe$_2$SiH did not work under the reaction conditions. Mechanistically, a reversible heterolytic Si–H bond cleavage by the polar Ru–S bond of the catalyst was proposed and tested experimentally affording sulfur stabilized silicon cation. The following Friedel-Crafts reaction transferred the silyl group to indoles leading to the Wheland intermediate, which was deprotonated by the weakly basic sulfur atom. The resulting Ru(H)–S(H) species immediately released dihydrogen to regenerate the initial catalytic ruthenium species.

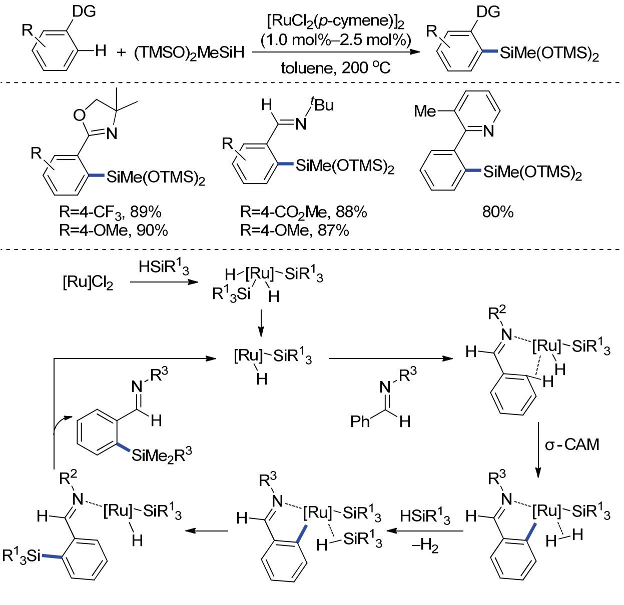


Scheme 20 Ru-catalyzed C–H sillylation of indoles via Friedel-Craft mechanism by Oestreich and Tatsumi.

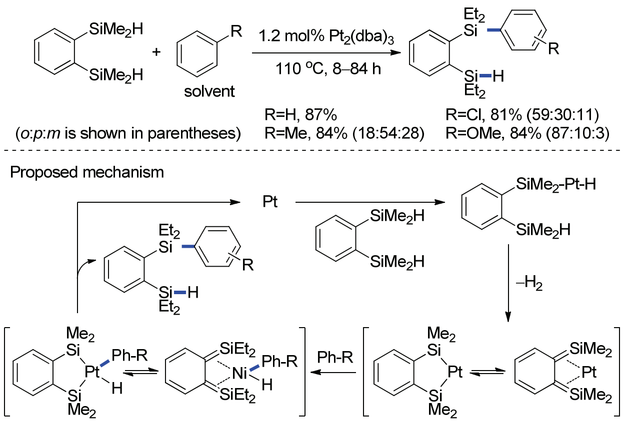
In 2012, Murata *et al.* [22] disclosed a Ru-catalyzed dehydrogenative aromatic C–H silylation reaction of 1,1,1,3,5,5,5-heptamethyltrisiloxane and arenes bearing *ortho*-directing groups under harsh conditions (Scheme 21). This method is applicable to aryloxazolines, arylimines, and arylpyridines. In all cases, only monosilylated products were obtained. Through DFT calculations, the authors thought the hydride silyl ruthenium species was the active catalyst, which coordinated with the nitrogen atom and C–H bond of the imine. The ensuing σ-complex-assisted metathesis (σ-CAM) occurred to give aryl silyl ruthenium species, which underwent reductive elimination after oxidative addition of hydrosilane affording C–H silylated product and regenerating hydride silyl ruthenium.

2.4 Pt-catalyzed silylation

In 1990s, Tanaka and coworkers [23] first reported the direct aromatic C–H silylation via platinum catalysis. Specifically, they demonstrated $Pt_2(dba)_3$-catalyzed silylation reactions of simple arenes with *o*-bis(dimethylsilyl)benzene (Scheme 22) [23a]. High yield of the phenylsilane product was obtained for benzene. However, a mixture of *o*-, *m*-, and *p*-silylated arenes were found for mono-substituted benzenes. Mechanistically, bis(silyl)platinum species was deemed as the possible reaction intermediate, which underwent oxidative addition with arenes affording arylhydroplatinum species. Metathesis of this intermediate gave final C–H silylated product and regenerated active platinum species.



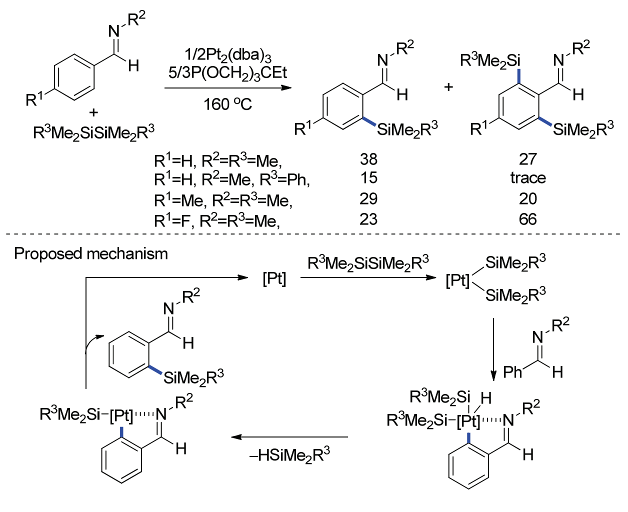
Scheme 21 Ru-catalyzed aromatic C–H silylation with trisiloxanes by Murata.



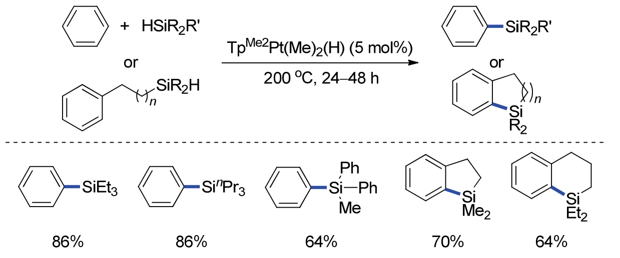
Scheme 22 Pt-catalyzed C–H silylation of simple arenes with silanes by Tanaka.

Two years later, they described platinum-catalyzed regioselective C–H silylation of *N*-benzylidene-methylamine with disilanes at high temperature (Scheme 23) [23b,23c]. Even though the silylated sites were controlled at the *ortho*-positions, a mixture of mono- and bis-silylated imine was obtained. Utilizing an excess amount of arenes enhanced the reaction chemoselectivity for the mono-silylated products, while bis-silylated arenes became the major products employing an excess amount of organodisilanes. The key C–H activation step was proposed to be an oxidative addition of C–H bond to the disilyated platinum intermediate.

In 2005, the Hartwig group disclosed a $\mathrm{Tp^{Me2}Pt(Me)_2(H)}$-catalyzed dehydrogenative coupling of hydrosilanes with arenes at 200 °C without any hydrogen acceptor (Scheme 24) [24]. The covalent ligand R in the $\mathrm{Tp^{Me2}Pt(R)(R')(H)}$ precatalyst played an important role in this catalytic system, and R=R′=Me proved to be the best. Alkylsilanes and arylalkylsilanes are suitable substrates for this reaction. However, *tert*-butyldimethylsilane bearing large steric hindrance and dichlorophenylsilane did not work well under these conditions. Furthermore, the tolerance of functional groups was not high, and regioisomers would be achieved for substituted arenes. Of note, the intramolecular dehydrogenative cyclization also proceeded under the same conditions to give five- and six-membered cyclic organosilanes.



Scheme 23 Pt-catalyzed C–H silylation of arylimines with disilanes by Tanaka.

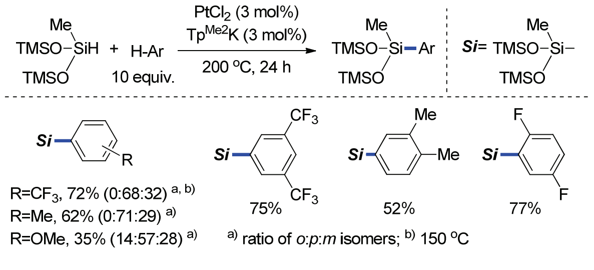


Scheme 24 Pt-catalyzed inter- and intramolecular silylation of arenes with silanes by Hartwig.

In 2007, Murata and coworkers [25] reported the direct C–H silylation of arenes with 1,1,1,3,5,5,5-heptamethyltrisiloxane under the catalysis of the $\mathrm{PtCl_2}$ and $\mathrm{Tp^{Me2}K}$ (Scheme 25). The formation of disilylated products were suppressed completely by utilizing an excess amount of arenes. However, a mixture of *meta*- and *para*-silylated regioisomers were obtained when mono-substituted arenes were used and the ratio of these product did not reflect the electronic characteristics of the substituents on arenes. In general, the electron-deficient arenes were more reactive than the electron-rich ones. Furthermore, the regioselectivity for the reactions of disubsitituted arenes might be controlled by the steric effect. The thus obtained arylsiloxanes could be used for the palladium-catalyzed Hiyama coupling reactions.

2.5 Sc-catalyzed silylation

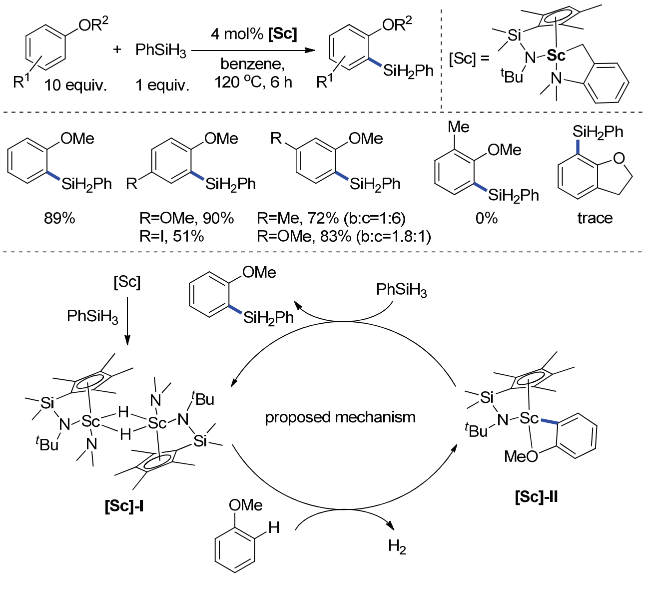
In 2011, Hou *et al.* [26] described an *ortho*-regioselective C–H silylation of alkoxy-substituted benzene derivatives catalyzed by a half-sandwich scandium complex (Scheme 26). The hydrogen acceptor was not required for this silylation reaction to achieve high conversion. The regioselectivity of the C–H silylation was controlled by the interaction between the methoxy group and the Sc atom in the catalyst. Halogen functionalities could be well tolerated in this protocol. Two regioisomers were obtained for the anisoles



Scheme 25 Pt-catalyzed C–H silylation of arenes with trisiloxanes by Murata.

bearing *meta*-substituted groups. However, the *ortho*-substituents severely deteriorated the reactivity possibly due to the steric hindrance in C–H activation and/or C–Si formation steps as the authors shown in stoichiometric reactions of these substrates. Also, the resting state of the active Sc catalyst and the cycloscandium complex via C–H activation were isolated in stoichiometric reactions. Based on these results, together with the KIE study and reaction kinetics, a possible reaction mechanism was proposed. The precatalyst **[Sc]** reacted with phenylsilane giving scandium-hydride complex **[Sc]-I**, which underwent *ortho*-C–H bond activation to afford cycloscandium complex **[Sc]-II** with release of H_2. The intermediate of **[Sc]-II** underwent σ-bond metathesis reaction with phenylsilane leading to C–H silylated anisole and regenerating hydride **[Sc]-I**. The authors believed that the coordination of anisole with **[Sc]-I** was the rate-limiting step of the whole catalytic cycle based on the reaction kinetic study.

So far, there are five kinds of transition metals (Ir, Rh, Ru, Pt, and Sc) which have been shown to catalyze the silylation reactions of inert C(sp^2)–H bonds. Among them, Pt-catalyzed protocols generally required very high termperature (160–200 °C) except the case using a special silylative reagent [23]. The only example of Sc-catalysis in C–H silylation demonstrated a unique reactivity, yet was limited to anisole substrates [26]. In contrast, the Ir-, Rh-, and Ru-catalyzed procedures displayed wider substrate scopes, milder reaction conditions, and better regio-control. Of particular note, the C–H silylation of simple arenes could be achieved at 45 °C with excellent regioselectivity by using the rhodium catalyst with phosphine ligands [18]. Another promising set is the combination of iridium catalysts with 1,10-phenanthroline/bipyridine ligands, which has shown competitive reaction performance compared with the rhodium system.



Scheme 26 Scandium-catalyzed silylation of aromatic C–H bonds by Hou.

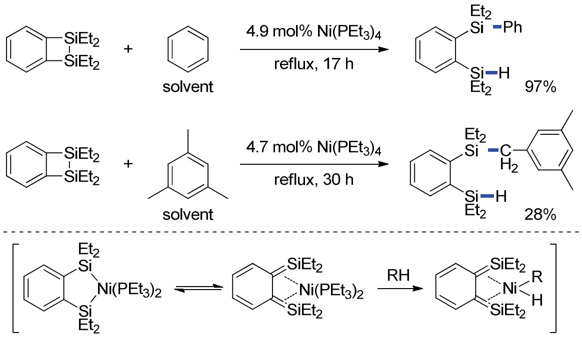
3 Silylation reaction of C(sp^3)–H bonds

The activation of C(sp^3)–H bonds, followed by incorporation of various functional groups, is still of great challenge in synthetic organic chemistry. Among various C–H functionalization reactions, the transition metal catalyzed silylation reactions have caught much attention because the resulting silylated products can be easily transferred to a wide range of useful compounds via reactions such as Tamao-Fleming oxidations, cross-coupling reactions, and fluoride-mediated functionalizations.

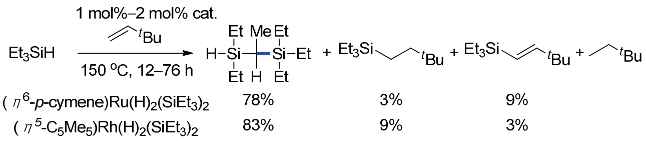
In 1992, Ishikawa and coworkers [27] discovered that under the catalysis of tetrakis(triethylphosphine)nickel 3,4-benzo-1,1,2,2-tetraethyl-1,2-disilacyclobutene reacted with benzene giving the aromatic C–H activation adduct in excellent yield (Scheme 27). Meanwhile, the use of mesitylene led to the C(sp^3)–H silylation product in low yield. The reaction was believed to occur through the oxidative addition of C–H bonds to the key *o*-quinodisilane nickel complex.

Two years later, Berry and coworkers [28] described a dehydrogenative dimerization of triethylsilane via C(sp^3)–H silylation utilizing ruthenium or rhodium complexes like (η^6-*p*-cymene)$Ru(H)_2(SiEt_3)_2$ and (η^5-C_5Me_5)$Rh(H)_2(SiEt_3)_2$ as catalysts in the presence of 3,3-dimethylbut-1-ene as a hydrogen acceptor (Scheme 28). An intermediate of η^2-silene complex, generated by β-hydrogen elimination from a silyl group, was deemed to be involved in the reaction mechanism.

In 2003, Tilley's group [29] reported a dehydrogenative C–H silylation of methane (CH_4) with H_2SiPh_2 under high pressure (150 atm of methane) using the Sc-catalyst (Eq.



Scheme 27 Ni-catalyzed silylation of benzylic C–H bonds by Ishikawa.



Scheme 28 Ru- or Rh-catalyzed dimerization of triethylsilane via C–H silylation by Berry.

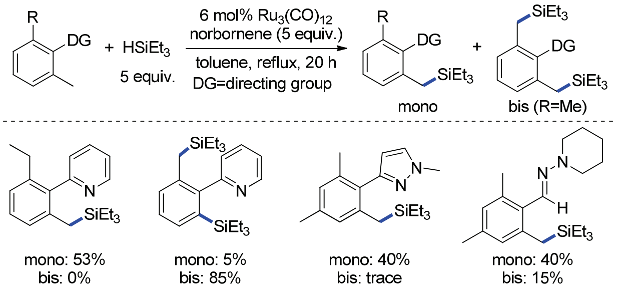
(2)). The authors believed the catalytic cycle of this reaction involved only σ-bond metathesis steps. After this prominent example, many catalyst systems of transition metals, such as Rh, Ru, and Ir, have been developed for the C–H silylation of benzylic or simple alkyl C(sp^3)–H bonds.

$$\mathrm{Ph_2SiH_2} + 150\ \mathrm{atm\ CH_4} \xrightarrow[\mathrm{C_6H_{12}},\ 80\ ^{\circ}\mathrm{C},\ 7\ \mathrm{days}]{10\%\ [\mathrm{Cp^*{}_2ScMe}]} \mathrm{Ph_2MeSiH} + \mathrm{H_2} \qquad (2)$$

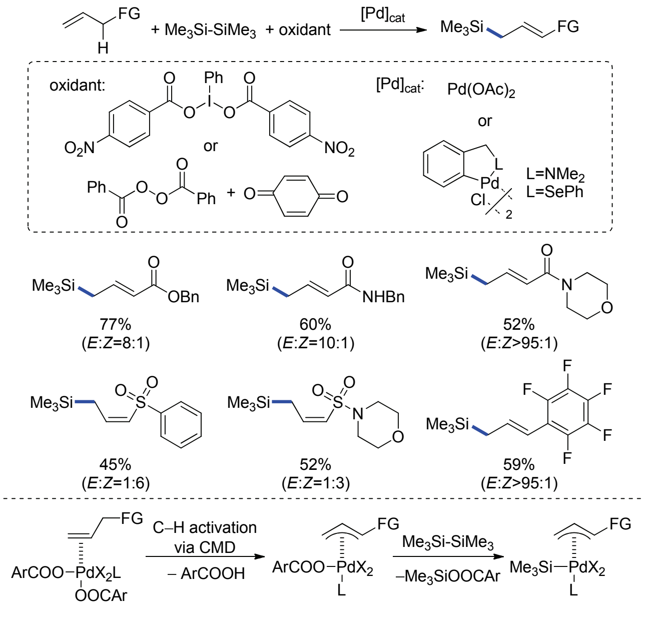
In 2004, Kakiuchi and coworkers [30] reported a chelation-assisted silylation reaction of benzylic C–H bonds with hydrosilanes utilizing $Ru_3(CO)_{12}$ as a catalyst and norbornene as a hydrogen acceptor (Scheme 29). Employing bulky hydrosilanes like $HSiPh_3$ led to the selective formation of a mono-silylation product, albeit in low yield. For the most reactive $HSiEt_3$, mono- and bis-silylated products were obtained. The steric hindrance at the benzylic position as well as the electronic effect affected the reactivity. As a result, secondary C(sp^3)–H bonds were not reactive. Aromatic C–H bonds demonstrated better reactivity than that of primary C(sp^3)–H bonds. Furthermore, arenes bearing other directing groups were also amenable to this protocol.

In 2011, Szabó and coworkers [31] disclosed the first Pd-catalyzed oxidative allylic C–H bond silylation with hexamethyldisilane as the silylation reagent (Scheme 30). The reaction used the hypervalent iodine(III) reagent as the most efficient oxidant thus a hydrogen scavenger being not necessary. Only terminal olefins were applicable to this protocol giving linear allylsilanes with excellent regioselectivity and moderate to good stereoselectivity. A Pd(II)/Pd(IV) catalytic cycle was proposed in which the Pd(IV)/olefin intermediate underwent the allylic C–H bond cleavage via a concerted deprotionative metalation mechanism. The resulting π-allyl Pd(IV) species ascribed for the observed linear regioselectivity in the reductive elimination step forming the C–Si bond. Also, the isomerization of the allyl moiety led to the production of both *E*- and *Z*-isomers.

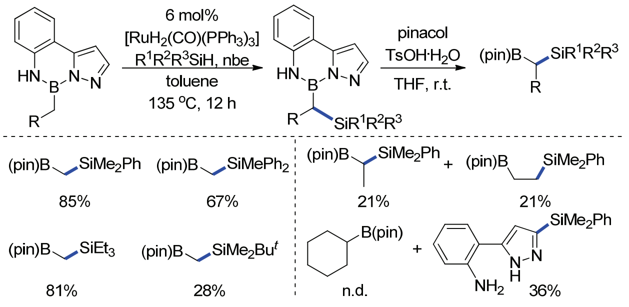
Almost at the same time, a Ru-catalyzed C–H silylation reaction of methylboronic acid with hydrosilanes using a removable directing group, 2-pyrazol-5-ylaniline (pza), was reported by Suginome *et al.* (Scheme 31) [32]. $[RuH_2(CO)(PPh_3)_3]$ showed the best performance among the catalysts screened. Several hydrosilanes were amenable to this reaction except for the steric demanding *t*-$BuMe_2SiH$. The ethylboronic acid derivative gave a mixture of 1- and 2-silylated products. When cyclohexylboronic acid was applied to this protocol, the silylation occurred only on the pyrazolyl ring, rather than the cyclohexane ring.



Scheme 29 Ru-catalyzed benzylic C–H silylation by Kakiuchi.



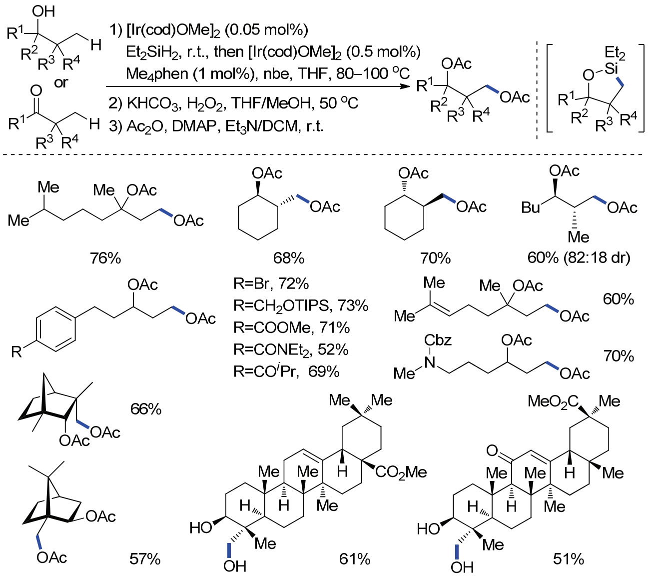
Scheme 30 Pd-catalyzed oxidative allylic C–H silylation by Szabó.



Scheme 31 Ru-catalyzed α-silylation of alkylboronic acids by Suginome.

Recently, the Hartwig group has made a series of advances on silylation of unactivated C(sp^3)–H bonds. In 2012, they [33a] reported a regioselective silylation of primary C(sp^3)–H bonds at the γ-position to a hydroxyl group with the use of an iridium-phenathroline catalyst and a hydrosilane reagent (Scheme 32). The C–H silylation products, oxasilolanes, could be easily oxidized to 1,3-diols without isolation. Both tertiary and secondary alcohols are suitable substrates for this transformation. *Trans*- and *cis*-2-methylcyclohexanols gave similar yields of the corresponding products. Good diastereoselectivity was obtained for the reaction of the substrate bearing diastereotropic methyl groups. The reaction sequence tolerated a range of functional groups, such as bromide, ester, and olefin. It is noteworthy that this protocol could be applicable to the functionalization of natural products containing hydroxyl or carbonyl groups such as (+)-fenchol and methyl oleante.

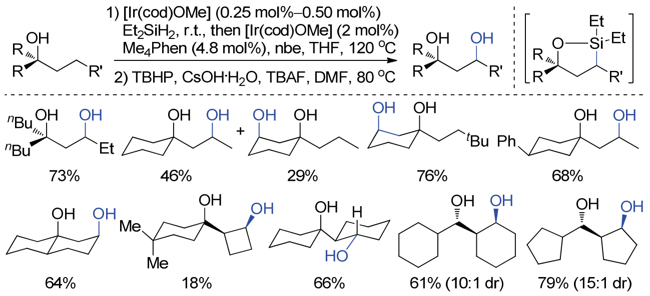
Nevertheless, the above strategy was limited to primary



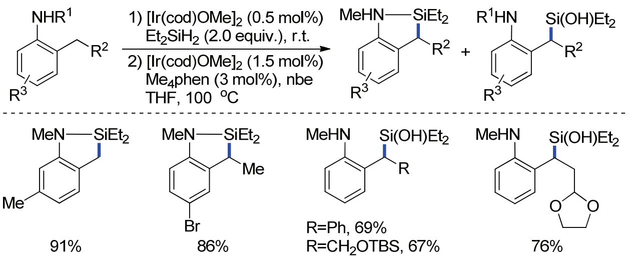
Scheme 32 Ir-catalyzed hydroxyl-directed γ-oxygenation via intramolecular silylation reactions by Hartwig.

C–H bonds. To overcome this inherent shortcoming, the same group [33b] developed another Ir-catalyzed silylation of secondary aliphatic C–H bonds affording 1,3-diols (Scheme 33). The regioseletivity was mainly dictated by the steric environments of the targeted C–H bonds. Tertiary alcohols demonstrated better reactivity than that of secondary alcohols, in which only those bearing substituents β to the hydroxyl groups gave the expected results efficiently. Moreover, this secondary C–H silylation was proved 40–50 times slower than the above primary C–H siylation process. In the same year, they further reported the silylation of benzylic C–H bonds directed by a secondary amine (Scheme 34) [11]. The reaction had a good tolerance of various functional groups and the resulted azasilolane ring opened to give silanols after purification through column chromatography.

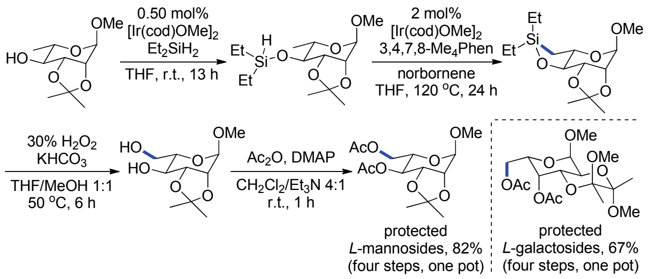
In 2012, Pedersen *et al.* [34] successfully extended Hartwig's method of diol synthesis to access two types of carbohydrates from 6-deoxysugars (Scheme 35). Specifically, the 2,3-protected methyl l-rhamnoside was treated with iridium catalyst and diethylsilane to obtain the silane-attached intermediate, which underwent intramolecular C–H silylation using Hartwig's procedure affording the cyclic silyl ether. The ensuing Fleming-Tamao oxidation gave diol, which was acetylated subsequently leading to the fully protected *L*-mannoside in 82% yield over four steps. With the similar strategy, protected *L*-galactoside was obtained from the corresponding 6-deoxysugar in 67% yield through four steps in one pot.



Scheme 33 Ir-catalyzed silylation of secondary C–H bonds of alcohols by Hartwig.

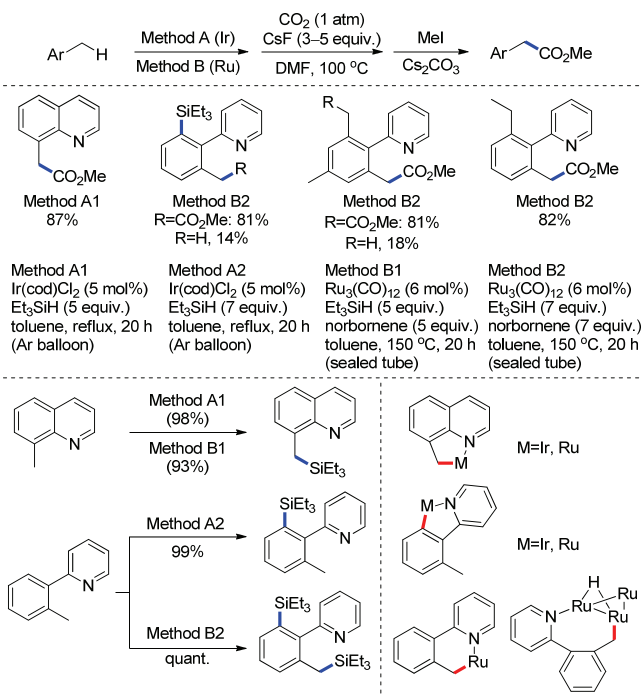


Scheme 34 Ir-catalyzed C–H silylation of *N*,2-alkylanilines by Hartwig.



Scheme 35 Synthesis of protected *L*-mannoside and *L*-galactoside through Ir-catalyzed C–H silylation/oxidation sequence by Pedersen and Bols.

In the same year, the group of Mita and Sato [35a] probed into a sequential protocol for benzylic C(sp^3)–H bond carboxylation with CO$_2$, which involves the Ir- or Ru-catalyzed C–H silylation and CsF-mediated carboxylation with CO$_2$ (Scheme 36). When 8-methylquinoline was used as substrate, the catalytic benzylic C–H silylations proceeded smoothly with both [Ir(cod)Cl]$_2$ and Ru$_3$(CO)$_{12}$ catalysts utilizing triethylsilane as the silylative resource. However, only aromatic C(sp^2)–H silylation occurred via a five-membered metallacycle for the substrate of 2-(σ-tolyl)pyridine when the Ir-catalyst was employed. The Ru-catalyst, in contrast, led to the silylation of both C(sp^2)–H and C(sp^3)–H bonds in 2-(σ-tolyl)pyridine, possibly due to the diverse five-, six-, or even seven-membered ruthenacycle intermediates formed by C–H activation. These results showed that the product distribution relied heavily on the active species of the catalyst. Meanwhile, the Ir-catalyzed C–H silylation occurred easily without any H$_2$ scavengers like norbornene which, however, were essential in the Ru-catalyzed silylation reactions. In the second carboxylation step, only the C(sp^3)–Si bond of C–H silylation products proceeded smoothly with the C(sp^2)–Si bond remaining intact, which



Scheme 36 Benzylic C–H silylation/carboxylation by Mita and Sato.

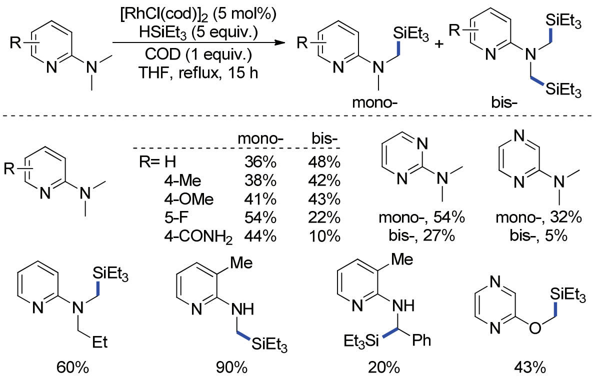
provided further synthetic handles for molecular manipulations.

In 2013, Mita *et al.* [35b] further developed methods for the silylation of C(sp^3)–H bonds adjacent to a nitrogen atom (Scheme 37). When the Ir-complex was used as catalyst for the silylation of 2-dimethylaminopyridine, a mixture of mono- and bis-silylated products as well as other byproducts was detected. As a result, it was difficult to isolate the silylated products after reaction. However, the use of Rh-catalyst delivered exclusively silylated products. Electron-rich substituents on the pyridine skeleton led to high conversion of substrates and bis-silyated products were obtained as major products, while mono-silylated products became to dominate when electron-withdrawing groups were utilized for the pyridine substrates. Other directing groups such as pyrimidine and pyrazine worked also well in this protocol. The primary C–H bond was selectively silylated in the presence of the secondary C–H bonds adjacent to the *N*-atom. For substrates bearing only one substituent on nitrogen, the 3-poisitioned substitutent on the pyridine ring proved to be essential for the success of C–H silylation due to the prohibition of *N*-silylated product by steric effect. This reaction was also applicable to the C–H bonds α to an oxygen atom.

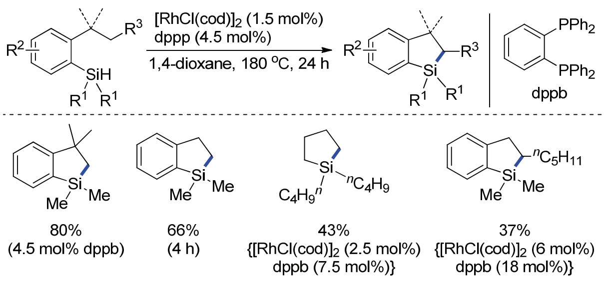
In the same year, Kuninobu *et al.* [36] developed a rhodium-catalyzed intramolecular silylation of unactivated C(sp^3)–H bonds in a regioselective manner (Scheme 38). The C(sp^3)–H bonds of the tertiary butyl and linear ethyl groups could be easily silylated under the reaction conditions. Also, the primary C(sp^3)–H bonds of the alkyl chain without incorporation of an aromatic ring was also amenable to this reaction. It is noteworthy that the regioselective C–H silylation could also proceed at the internal position of the alkyl chain, albeit with relatively high loading of the catalyst and ligand.

In 2014, Gevorgyan and coworkers [37] reported a novel strategy for the conversion of 1-alkenes into 1,4-diols via a three-step sequence, namely, auxiliary attachment/C–H silylation/oxidation (Scheme 39). The Si,N-type chelating group, *t*-butyl-picolylsilicon hydride, proved to be the best auxiliary, where the *t*-butyl group contributes to the stability of *t*-butyl-picolylsilane **3**. The picolyl substituent not only promoted the Si–H/C–H activation through the intermediate **4** but also facilitated the oxidation of the resulting silolane **5**. Of note, the key step of Ir-catalyzed intramolecular dehydrogenative silylation adopted the method developed by Hartwig and coworkers [33a].

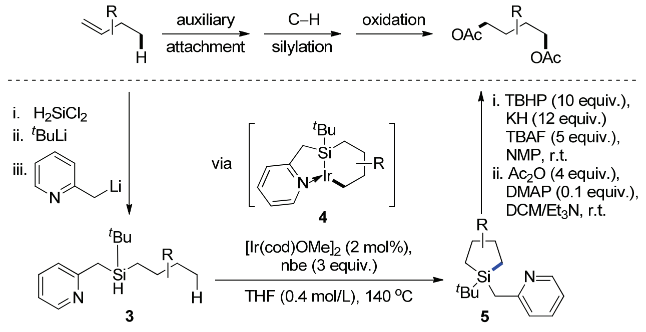
It can be seen that the direct silylation of unactivated C(sp^3)–H bonds has been less studied in comparison with that of inert C(sp^2)–H bonds. Only few sporadic examples were reported using Ni-, Sc-, and Pd-catalysis for special substrates. The major work of C(sp^3)–H silylation focuses still on Ir-, Rh-, and Ru-catalytic systems, which are in close relation with those of C(sp^2)–H silylation. The Ir-catalyzed silylation of unactivated C(sp^3)–H bonds in flexible aliphatic alcohols represents the most substantial breakthrough which may find diverse applications in complex molecule synthesis [33].



Scheme 37 Rh-catalyzed dehydrogenative silylation of C(sp^3)–H bonds adjacent to N-atoms by Mita and Sato.



Scheme 38 Rh-catalyzed intramolecular silylation of unactivated C(sp^3)–H bonds by Kuninobu and Takai.



Scheme 39 Conversion of 1-alkenes to 1,4-diols via Ir-catalyzed intramolecular silylation of unactivated C(sp^3)–H bonds by Gevorgyan.

4 Conclusions

In this paper, the developments of the silylation of inert C(sp^2 or sp^3)–H bonds via transition metal catalysis were summarized. Since the seminal discovery by Curtis in 1982, where only very low yield of the C–H silylation product was obtained at high temperature and after long reaction time (Eq. (1)), great success has been achieved in this field. Various transition metals such as Ir, Ru, Rh, and Pt. could be used as catalysts for C–H silylation processes. The reaction efficiency has been greatly improved in terms of the substrate diversity, reaction temperature, reaction time, and stoichiometry of arenes. Heretofore, the regioselectivity of the C–H silylation is usually controlled either by steric effects originating from catalysts, ligands, silyl sources, and even substrates, or by directing groups such as hydroxy groups, amino groups, oxygen or nitrogen atoms on heterocycles. The C–H silylation reactions have provided an alternative and powerful tool for synthesis of complex molecules like natural products and sugars.

Nevertheless, challenges still remain in this field: (1) relatively high temperature (around 100 °C) is often needed for the key silylation step of both C(sp^2)–H and C(sp^3)–H bonds and mild reaction conditions are required; (2) the C(sp^3)–H silylation is limited to intramolecular reactions; (3) the diverse site-selectivity beyond the steric effects and directing groups is desirable in particular for complex molecules bearing multiple C–H bonds; (4) asymmetric C–H silylation is still in its infancy. Judicious design and development of efficient transition metal catalysts might be the key to overcome the abovementioned challenging problems. So far, the noble transition metal catalysts predominate in the C–H silylation reactions. Due to the huge potentials of earth's abundant first-row transitional metals (Fe, Mn, Cu, etc.) [38], the explorations on their novel reactivities in C–H silylation reactions might open a new door for this field.

This work was financially supported by the National Natural Science Foundation of China (21322203, 21272238, 21472194), and the National Basic Research Program of China (2012CB821600).

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