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Construction of Si-Stereogenic Silanes through C–H Activation Approach

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The asymmetric synthesis of Si-stereogenic silanes has attracted great attention due to the increasing values of Si-containing functional molecules in synthetic chemistry, medicinal chemistry, and material chemistry. Merging organosilicon chemistry with transition-metal-catalyzed C–H approach has led to rich sets of new reactions holding great synthetic values. This Minireview aims to summarize the advances in the construction of Si-stereogenic silanes through the transition-metal-catalyzed C–H activation approach.

1. Introduction

Silicon element is the second most abundant element after oxygen in the earth's crust, and the most abundant silicon-containing minerals in nature are sand and inorganic silicates.[1] However, there is no natural organosilicon compound has been reported so far, although silicon is not absence in organisms, normally as an important structural building block for the skeletons of marine organisms such as diatoms, sponges, and radiolarians.[2] Despite of the absence of organosilicon compounds in nature, organosilicon compounds are widely utilized as sealants and adjuvants on the scale of megatons/year for construction, agriculture, cosmetic, automotive, and high-performance aerospace applications[3] since the synthesis of the first organosilicon compound in 1860s. In addition, organosilicon compounds found many applications in the fields of organic synthetic chemistry,[4,5] material science[3,4,6] and medicinal chemistry[7] (Figure 1). For instance, the induction of silicon on optoelectronic materials could lead to low LUMO energy level via the σ^*-π^* conjugation, which has been widely leveraged.[6] Furthermore, the 'silicon-carbon switch strategy' has also received increasing attention in medicinal chemistry,[7] due to the low toxicity and favorable metabolic profiles of silicon-containing compounds.

Among those organosilicon compounds, chiral organosilanes play more and more important roles as versatile chiral precursors, chiral auxiliaries and chiral catalysts in asymmetric synthesis.[8] For example, the Si-centered spirocyclic scaffolds could serve as the promising platforms for chiral catalyst and ligand development reported by the Wang group.[9] However, methods for the efficient construction of Si-stereogenic organosilanes are significantly less demonstrated in comparison to their congeners, carbon-stereogenic compounds.[10] The construction of carbon-centered chirality largely relies on differentiating the enantiotropic faces of the prochiral carbon-carbon and carbon-heteroatom double bonds, which is rare for the construction of Si-centered chirality due to the usually unavailable of the stable Si(sp^2)-hybridized silicon-carbon or silicon-heteroatom double bonds. Typically, the access to Si-stereogenic silanes relies on the chiral resolution with stoichiometric chiral regents or auxiliaries[11] pioneered by Sommer in 1960s.[12] Recently, the asymmetric synthesis of enantioenriched Si-stereogenic silanes has become one of the hottest areas via the strategies of transition metal-catalyzed enantioselective desymmetrization reactions of prochiral organosilanes,[10,13] since Corriu[13a] and Kumada[13b] independently reported the Rh-catalyzed desymmetrization of prochiral diorganodihydrosilanes.

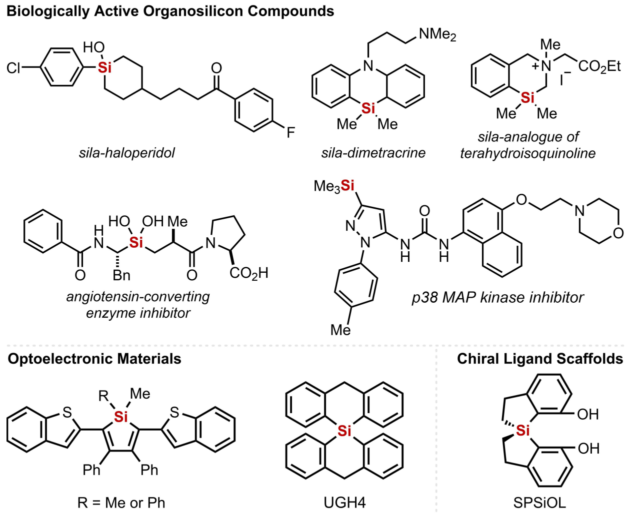

Figure 1. Functional organosilicon compounds.

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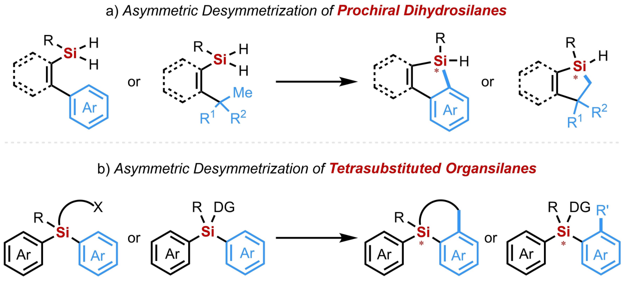
The transition metal catalyzed C–H activation reactions have opened a new dimension in synthetic organic chemistry due to the step- and atom-economy in the construction of C–C bonds and C–X bonds from ubiquitous C–H bonds in organic molecules.[14] The induction of chiral Si-stereogenic silanes via transition metal-catalyzed C–H activation approach is an elegant and attractive solution, allowing the construction of chiral Si-stereogenic silanes in shorter steps from simple starting materials. The earliest enantioselective construction of Si-stereogenic silanes via C–H activation approach has been reported by Shintani, Hayashi, and their co-workers in 2012.[15] Almost in the same timeline, Kuninobu, Takai and coworkers have developed Rh-catalyzed intramolecular C–H dehydrogenative silylation with diorganodihydrosilanes for the construction of optical spirosilabifluorene.[16,17] Following those pioneering works, diverse sets of protocols for the synthesis of enantioenriched Si-stereogenic organosilanes via C–H activation approach have been witnessed in the past decade. In general, two strategies have been demonstrated in the literatures: 1) the asymmetric desymmetrization of prochiral diorganodihydrosilanes via transition metal-catalyzed dehydrogenative C–H silylation reaction (Scheme 1a); 2) the asymmetric desymmetrization of tetrasubstituted organosilanes via transition metal-catalyzed intramolecular or intermolecular C–H functionalizations (Scheme 1b). This minireview summarizes the advances in construction of Si-stereogenic silanes via this approach as well as the future perspective.


a) *Asymmetric Desymmetrization of Prochiral Dihydrosilanes*

b) *Asymmetric Desymmetrization of Tetrasubstituted Organsilanes*

Scheme 1. Construction of Si-stereogenic silanes via transition metal-catalyzed C–H activation approach.

2. Transition Metal-Catalyzed Asymmetric Desymmetrization of Prochiral Dihydrosilanes

In recent years, transition metal-catalyzed intramolecular C–H silylation reaction have been demonstrated as a charming manner for construction of Si-stereogenic silanes pioneered by Kuninobu and Takai.[16] In 2013, they reported the first example of Rh-catalyzed double Si–H/C–H dehydrogenative coupling reaction to access axially chiral spirosilabifluorenes, which are a class of attractive organic material molecules (Scheme 2).[16a] Employing bis(2-arylphenyl)dihydrosilanes as substrates and (*R*)-BINAP (**L1**) as the chiral ligand, the corresponding spirosilabifluorenes were obtained in high yields and good ee values (up to 81 % ee). Three years later, Murai, Takai and coworkers have improved the enantioselectivity to 95 % ee by lowering the reaction temperature from 135 °C to 70 °C.

Stemming from this study, Murai and Takai described the mechanistic insights into the construction of a quaternary silicon chiral centers in 2016.[16b] This reaction starts with the oxidative addition of a Si–H bond to the rhodium center to generate intermediate **int-1**, then involves oxidative addition to aryl C–H bonds and reductive elimination to form the corresponding C–Si bond. Monohydrosilane intermediate **int-3** undergoes the similar elementary steps to form the chiral spirosilabifluorene and the catalytic cycle is completed (Scheme 3). Due to the isolation of chiral monohydrosilane intermediates (**int-3**) with the same ee values as the final product, the chirality of the spirosilabifluorenes is most likely determined at the first dehydrogenative cyclization step, and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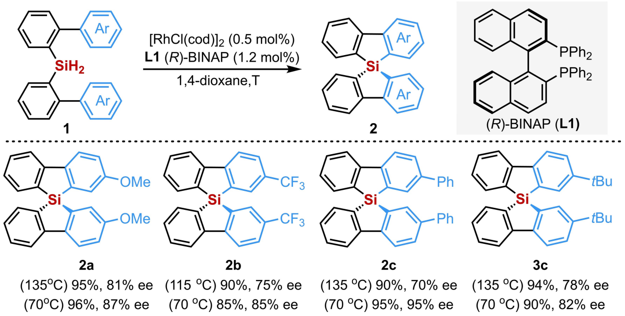
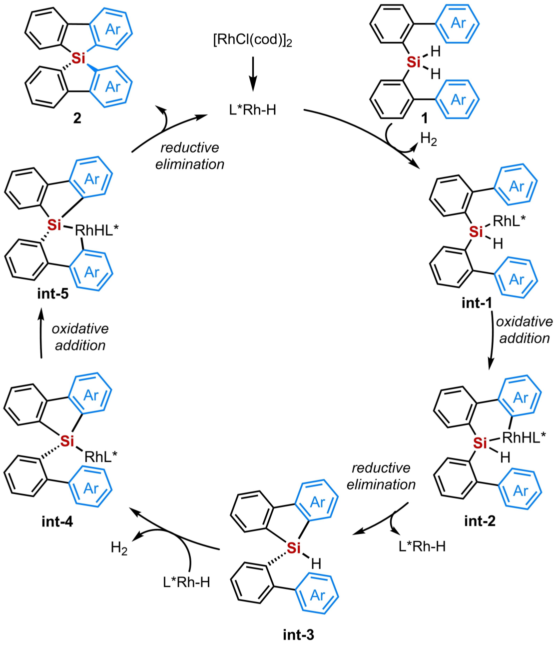
Yichen Wu received her PhD degree from the Institute of Chemical Research of Catalonia, Spain (ICIQ) in 2017 under the supervision of Prof. Alexandr Shafir. From 2018, she joined Prof. Wang' group at the Shanghai Institute of Organic Chemistry (SIOC) first as a postdoctoral researcher and now as an assistant professor. Her current research interests focus on the construction of chiral silicon compounds.

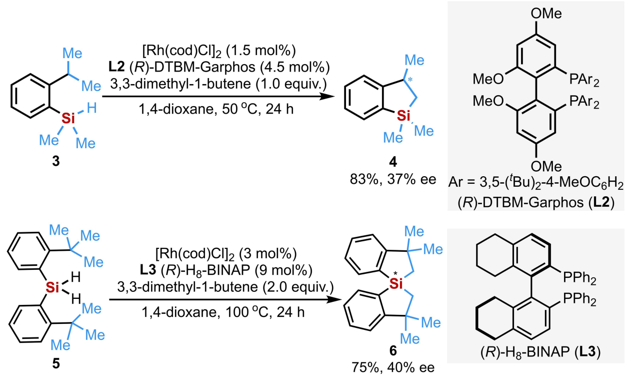

Peng Wang received his BS degree from Tianjin University in 2007, and completed his PhD under the supervision of Prof. Yong Tang at Shanghai Institute of Organic Chemistry (SIOC) in 2013. He joined SIOC as a full professor in early 2018 after carrying postdoctoral research with Prof. Jin-Quan Yu at the Scripps Research Institute (TRSI). His research group focues on transition metal catalysis and main group chemistry.



Scheme 2. Asymmetric synthesis of spirosilabifluorenes via rhodium-catalyzed Si–H/C–H dehydrogenative coupling.



Scheme 3. Proposed mechanism for the synthesis of axially chiral spirosilabifluorenes.



Scheme 4. Rhodium-catalyzed asymmetric C(sp^3)–H silylation.

the chirality transferring from silicon center to axial is retentive in the second dehydrogenative cyclization.

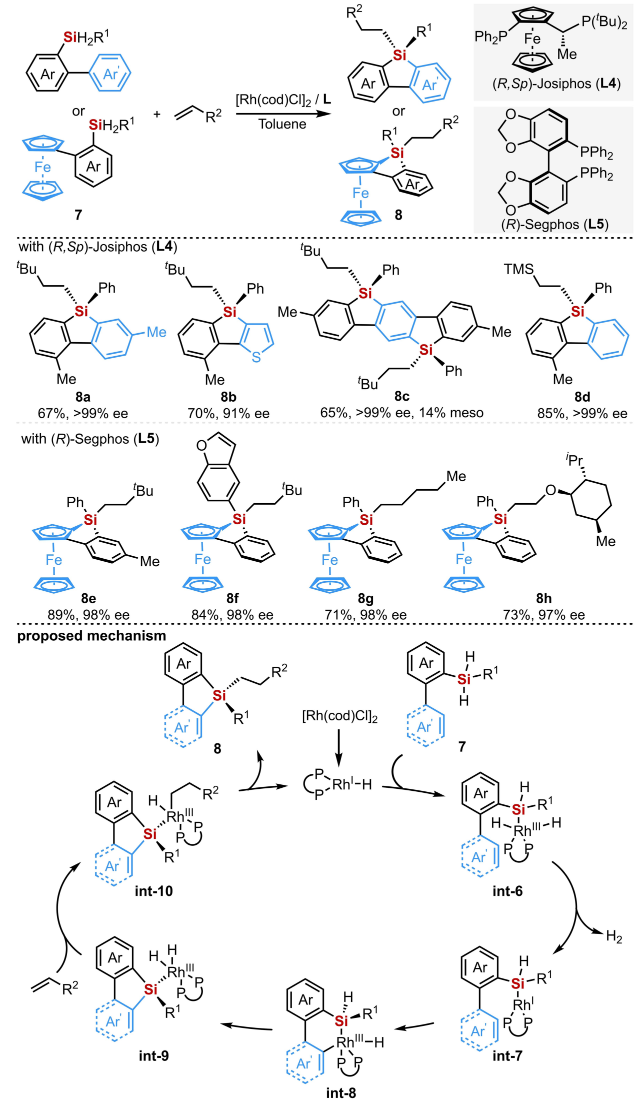
In 2015, the same group has extended this concept for the synthesis of tetrasubstituted silicon-stereogenic silanes via Rh-catalyzed dehydrogenative silylation of inert C(sp^3)–H bond.[17] With (*R*)-DTBM-Garphos (**L2**) as the optimal chiral ligand, this Rh-catalyzed intramolecular C(sp^3)–H silylation resulted in dihydrobenzosilole **4** in 83% yield and 37% ee (Scheme 4). Moreover, the axially chiral spirosilabiindane could also be obtained in 75% yield with 40% ee via double C(sp^3)–H silylation in the presence of (*R*)-H_8-BINAP (**L3**).

Last year, the group of C. He reported a Rh-catalyzed asymmetric synthesis of silafluorenes through tandem intramolecular C–H silylation with dihydrosilanes and sequentially intermolecular alkene hydrosilylation.[18] Mechanistic studies unveiled that this reaction underwent a Rh-catalyzed enantioselective desymmetrization of dihydrosilanes to access the unstable enantioenriched spirosilafluorene-based monohydrosilanes, which are in-situ transformed to the quaternary Si-stereogenic silanes in a stereospecific manner (Scheme 5). With (*R*,*Sp*)-Josiphos (**L4**) or (*R*)-Segphos (**L5**) as the chiral ligand, a wide range of enantioenriched 9-silafluorene derivatives and benzosilolometallocenes could be readily prepared in good yields with excellent enantioselectivities (up to 95% yield and >99% ee). Notably, this method is also suitable for the synthesis of optically pure silicon-bridged π-conjugated motifs, which might possess unique optoelectronic properties.[3]

Soon after, the same group extended this tandem process to construct chiral benzosiloles via Rh-catalyzed enantioselective intramolecular dehydrogenative C(sp^3)–H silylation and sequentially stereospecific alkenes hydrosilylation.[19] The alkene might play a dual role as the hydrogen acceptor in the first dehydrogenative cyclization, and as the reactant in the stereospecific hydrosilylation step (Scheme 6). In the presence of Josiphos-type ligand (**L4**), the reaction could proceed in good to excellent yields and enantioselectivities, providing a series of enantioenriched silicon-stereogenic benzosiloles.

As mentioned in the aforementioned reports, the monohydrosilanes formed in the transition metal-catalyzed dehydrogenative C–H silylation are normally unstable in the presence of transition metal catalysts at high temperature. Despite of this fact, Murai, Takai and coworkers have demonstrated the characterization of Si-stereogenic monohydrosilanes when shorten the reaction time during the mechanistic investigation of their Rh-catalyzed asymmetric intramolecular dehydrogenative C–H silylation.[16,17] The group of C. He also mentioned the isolation of the enantioenriched monohydrosilane intermediate in the Rh-catalyzed tandem intramolecular C–H silylation/alkene hydrosilylation process.[18,19] Those observations indicate the preparation of Si-stereogenic monohydrosilanes via transition metal catalysis is feasible.

Early this year, the asymmetric synthesis of chiral monohydrosilanes via Rh-catalyzed intramolecular C–H silylation approach has been finally realized by the group of W. He.[20] Using a combination of $[Rh(COD)Cl]_2$ and (*R*)-DTBM-Segphos (**L6**), a wide range of silicon-stereogenic spirosilabifluorene-cored and ferrocene-based monohydrosilanes were readily obtained in high yields and excellent enantioselectivities under

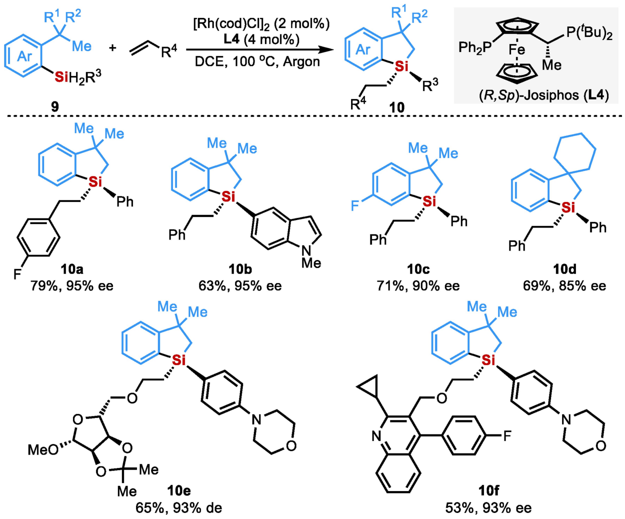


Scheme 5. Rh-catalyzed enantioselective tandem C–H silylation/alkene hydrosilylation.

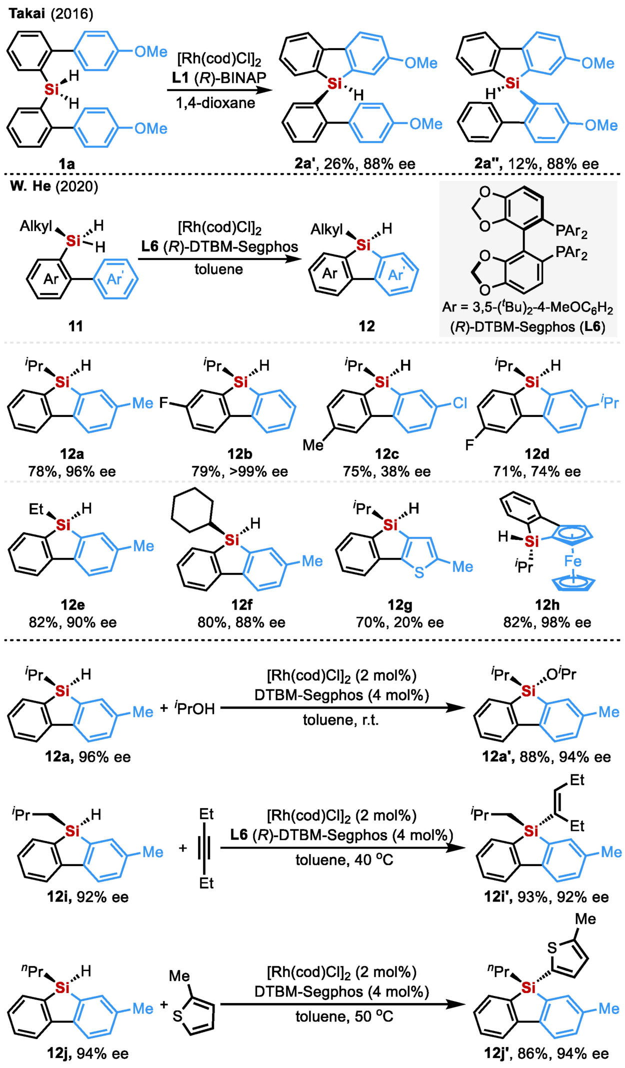
mild conditions (Scheme 7). Gratifyingly, silicon-stereogenic spirosilabifluorene-cored tetrasubstituted silanes could be obtained via stereospecific transformations of the Si–H bond, including alcoholysis with alcohol, hydrosilylation with ketone, alkene and alkyne, and dehydrogenative arylation with arene. Those stereospecific transformations showcased the importance of the construction of optically pure monohydrosilanes.

A proposed mechanism was showed in Scheme 8, which is similar to Takai's initial hypothesis. The reaction underwent a process of oxidative addition of Si–H with Rh(I)–H species to generate intermediate **int-11**, release of H_2 to afford Rh(I)–Si intermediate **int-12**, oxidative addition of the C(sp^2)–H to give Rh(III) species **int-13**, and finally reductive elimination to afford product (Scheme 8). The oxidative addition of Si–H was assumed as the enantioselective step.

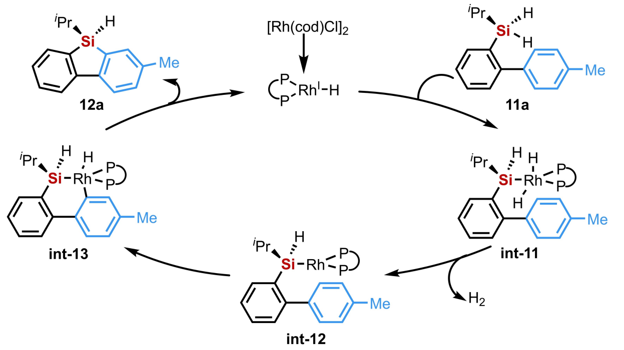
A slightly later, C. He group also described the asymmetric synthesis of 1*H*-benzosiloles and 1*H*-benzosilolometallocenes



Scheme 6. Rhodium-catalyzed cascade enantioselective silylation of C(*sp*^{3})–H with stereospecific alkene hydrosilylation.



Scheme 7. Rh-catalyzed intramolecular C–H silylation for the preparation of silicon-stereogenic monohydrosilanes.

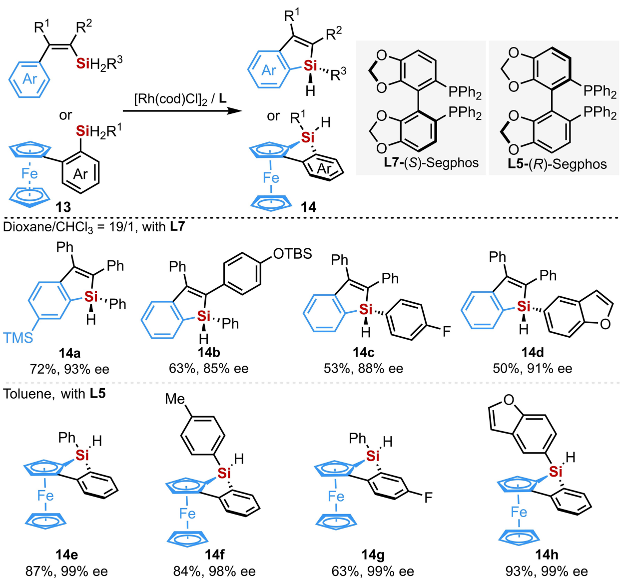


Scheme 8. Proposed mechanism for Rh-catalyzed intramolecular C–H silylation to construction of monohydrosilanes.

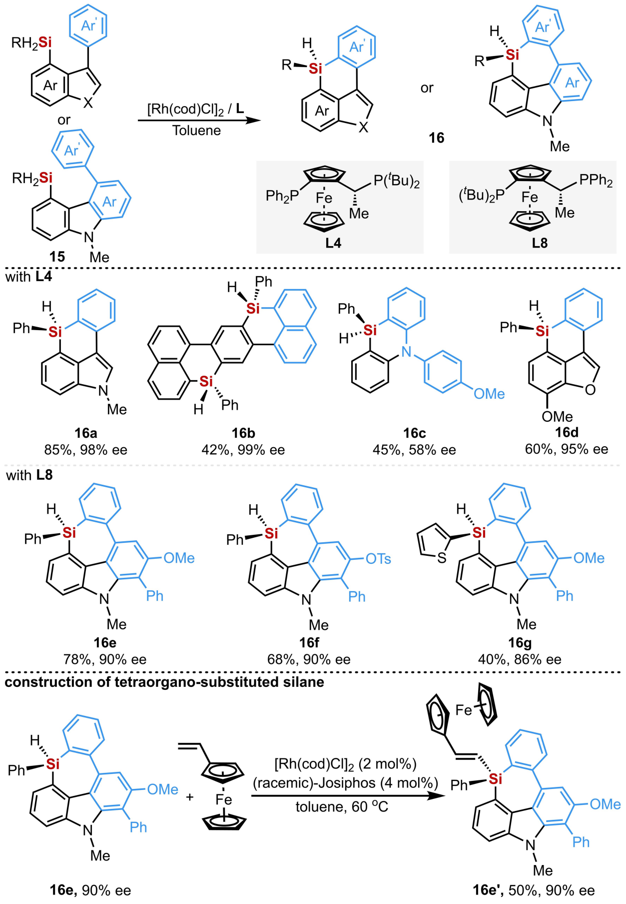
via a similar catalytic system (Scheme 9).[21] Using Segphos as ligand, the intramolecular asymmetric silylation of alkenyl C–H bond with dihydrosilanes are achieved in good yields with excellent stereo induction.

As the 9-silabifluorene motifs are an important class of optoelectronic materials, the synthesis of other silicon-containing π-conjugated silacycles is attractive, but remains a big challenge. The group of C. He applied the approach of Rh-catalyzed asymmetric dehydrogenative silylation to construct the six- and seven membered cyclic monohydrosilanes bearing a chiral silicon center (Scheme 10).[22] Preliminary photophysical properties investigations unveiled the promising potential as the optoelectronic material of this class of π-conjugated enantioenriched monohydrosilanes due to their bright blue fluorescence under UV light irradiation.

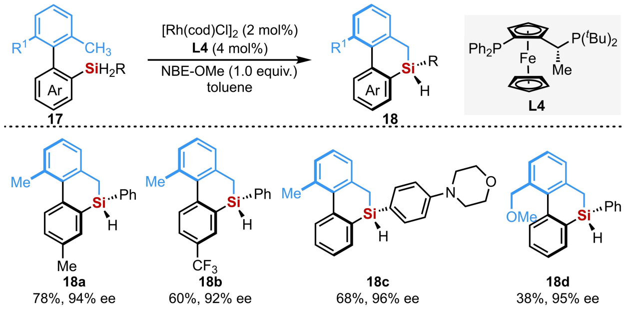
In 2021, He's group reported rhodium-catalyzed asymmetric synthesis of silicon-stereogenic dihydrodibenzosilines through intramolecule aliphatic C–H bond activation (Scheme 11).[23] A wide range of dihydrodibenzosilines containing both silicon-central and axial chiralities are conveniently constructed. The desymmetrization of 2,6-dimethyl biaryls via Rh-catalyzed intramolecular dehydrogenative C(sp^3)–H silylation with dihydrosilanes led to the observation of silicon center chirality to axially chirality relay phenomenon. In addition, the kinetic resolution of unsymmetrical biaryls also resulted in the desired dihydrodibenzosilines in 35%–42% yields with 83%–96% ee employing Josiphos-type as the chiral ligand.



Scheme 9. Synthesis of five-membered silicon-stereogenic monohydrosilanes.



Scheme 10. Preparation of silicon-stereogenic six- and seven membered monohydrosilanes.



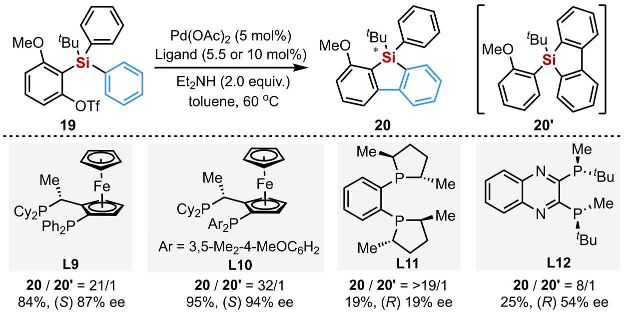
Scheme 11. Preparation of Si-stereogenic dihydrodibenzosilines.

3. Asymmetric Desymmetrization of Tetrasubstituted Organosilanes

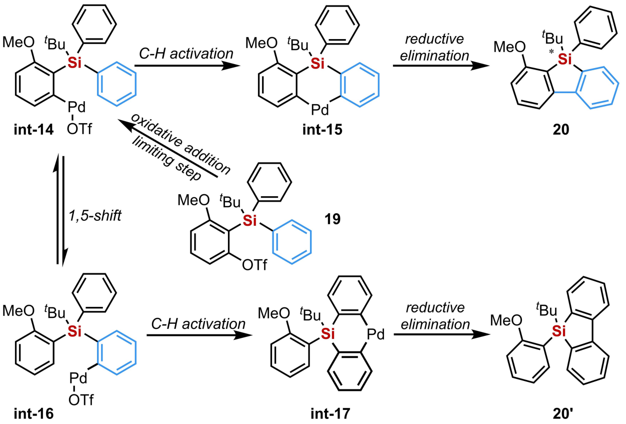
Since the first example of asymmetric synthesis of Si-stereogenic silanes via Pd-catalyzed intramolecular C–H arylation, asymmetric desymmetrization of tetrasubstituted organosilanes has been demonstrated as another efficient strategy for the preparation of cyclic and acyclic enantioenriched tetraorganosilanes. In the course, reaction patterns of both the Pd-catalyzed C–H functionalization and transition-metal catalyzed C–H silylation reaction are widely studied.

3.1. Desymmetrization via Pd-catalyzed intramolecular C–H cyclization

As mentioned previously, the group of Shintani and Hayashi reported the first asymmetric desymmetrization of prochiral 2-(diarylsilyl)aryl triflates through a palladium-catalyzed intramolecular C–H bond arylation,[15] following the non-asymmetric variant by Shimizu and coworkers.[24] The desired enantioenriched dibenzosilole **20** could be chemoselectively formed in 95% yield and 94% ee employing a Josiphos-type ligand ((*R*,*S*p)-**L10**) (Scheme 12). With this protocol, a series of enantioenriched dibenzosiloles could be synthesized in high efficiency and enantioselectivities during the optimization, an undesired nonchiral byproduct **20′** was also obtained.



Scheme 12. Synthesis of silicon-stereogenic dibenzosiloles via Pd-catalyzed asymmetric intramolecular C–H bond arylation.

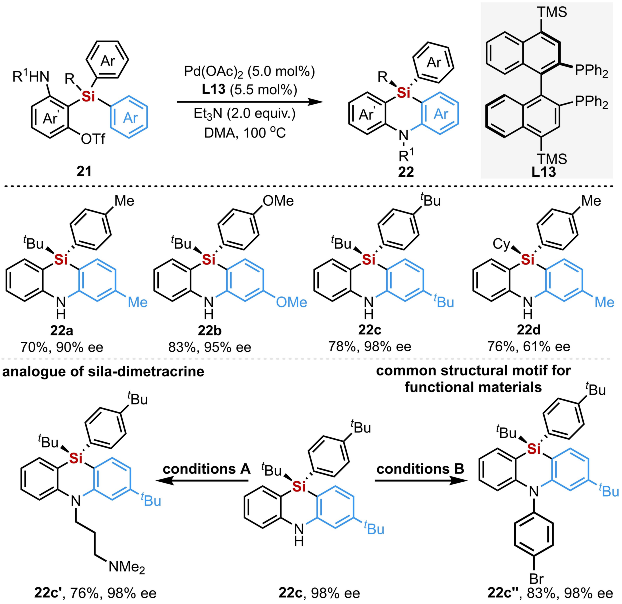


Scheme 13. Mechanism for Pd-catalyzed intramolecular C–H arylation.

Based on the kinetic isotopic effects, a proposed mechanism was showed in Scheme 13. Oxidative addition of aryl triflate to Pd(0) gave arylpalladium triflate intermediate **int-14**, followed by a base-assisted intramolecular C–H bond activation to produce intermediate **int-15**. The chiral dibenzosilole could be obtained via reductive elimination of intermediate **int-15**, along with the regeneration of Pd(0) catalyst. The undesired by-product **20′** could be elucidated by a 1,5-Pd migration process, which could be suppressed by using the bisphosphine ligands.

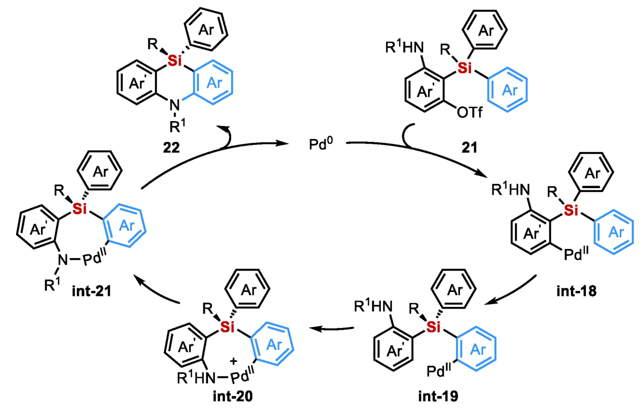
Inspired by the aforementioned undesired 1,5-Pd migration process, Shintani and Nozaki group described the asymmetric synthesis of silicon-stereogenic 5,10-dihydrophenazasilines with 4,4′-bis(trimethylsilyl) (*R*)-BINAP (**L13**) as the optimal ligand in which the 1,5-Pd migration was the key elementary step (Scheme 14).[25] This reaction presumably occurred by the oxidative addition of Pd(0) with aryl triflates, followed by 1,5-palladium migration to produce intermediate **int-19**. Then, intramolecular coordination of the amino group to the palladium center formed intermediate **int-20**, followed by deprotonation with triethylamine to give palladacycle intermediate **int-21**. Finally, the desired 5,10-dihydrophenazasiline was generated via reductive elimination of intermediate **int-21**, and Pd(0) was regenerated to finish the catalytic cycle (Scheme 15). The mechanistic investigations suggested that the 1,5-palladium migration was the enantiodetermining step.

As six-membered azacycles are distributed in biologically active molecules and functional materials, the enantioenriched 5,10-dihydrophenazasiline **22c** could be readily transformed to



Conditions A: (3-chloropropyl)dimethylamine hydrochloride (6.0 equiv.), NaH (12.8 equiv.), DMF, 50 °C
Conditions B: 1-bromo-4-iodobenzene (3.0 equiv.), Pd(OAc)$_2$ (20 mol%), Xantphos (20 mol%), NaO^{t}Bu (3.0 equiv.), dioxane, 100 °C

Scheme 14. Preparation of silicon-stereogenic 5,10-dihydrophenazasilines via 1,5-palladium migration process.

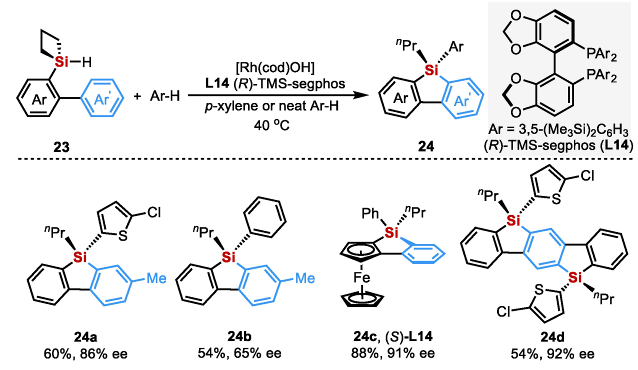


Scheme 15. Possible mechanism for synthesis of dihydrophenazasilines.

some drug or material counterparts without loss of its enantiomeric excess.

3.2. Desymmetrization via transition-metal-catalyzed intramolecular C–H silylation

In 2017, the group of W. He described a rhodium-catalyzed tandem silacyclobutane (SCB) desymmetrization/C–H silylation and intermolecular dehydrogenative silylation to prepare the chiral tetraorganosilanes[26a] (Scheme 16) following their initial finding of Rh-catalyzed intramolecular C–H silylation with silacyclobutanes.[26b] A wide array of dibenzosiloles with stereogenic quaternary silicon centers are obtained in good yields and enantioselectivities in the presence of Rh(I)/(*R*)-TMS-Segphos (**L14**)- catalytic system. In addition, this process is also suitable for the access of ferrocene-based benzosilole bearing both a stereogenic silicon center and planar chirality with high diastereoselectivity and enantioselectivity. Mechanistic studies disclosed that this reaction may proceed through Rh(I)–H enabled the silacyclobutanes opening/intramolecular C–H silylation process, followed by Si–H/C–H dehydrogenative arylation with simple arenes.[26c]

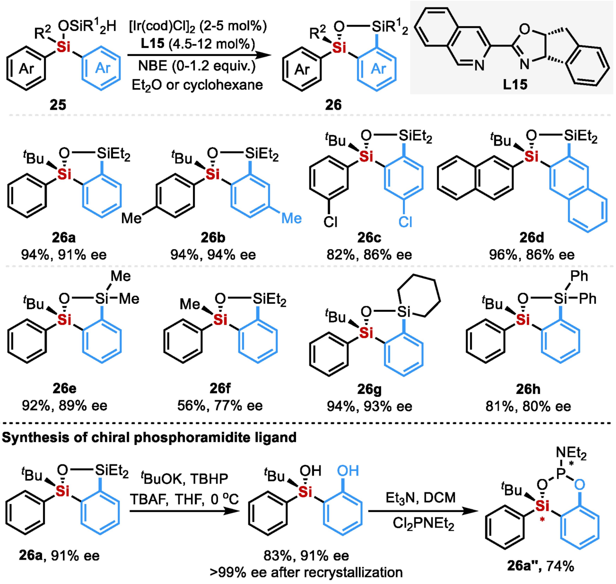


Scheme 16. Rhodium-catalyzed tandem silacyclobutane desymmetrization/C–H silylation and intermolecular dehydrogenative silylation.

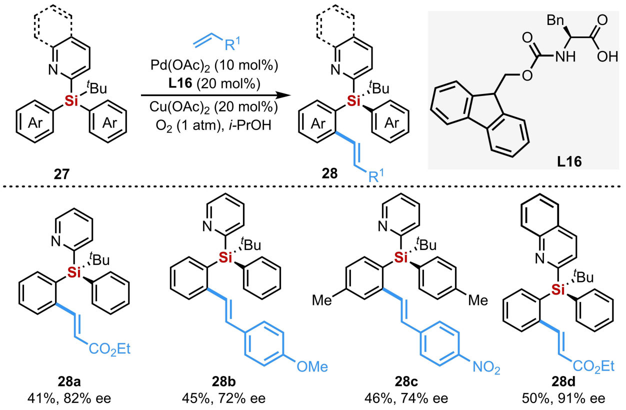
Inspired by Rh- or Ir-catalyzed Si–H/C–H dehydrogenative coupling silylation reactions to construct carbon-stereogenic diarylmethanols developed by Hartwig and Shi,[27] Zhao and coworkers recently reported iridium-catalyzed asymmetric desymmetrization of diarylsilanols with the same strategy (Scheme 17).[28] Notably, the Ir-catalyzed nonchiral variant of this reaction for synthesis of cyclic siloxanes has been previously reported by the Xu group.[29] With chiral ligand **L15**, the silicon-stereogenic tetrasubstituted cyclic siloxanes were accessible with excellent enantioselectivities (up to 95 % ee). Interestingly, an optically pure diol bearing a Si-stereogenic silanol structure could be synthesized upon Tamao-Fleming oxidation and recrystallization, which can be used as a precursor for the preparation of a class of chiral phosphoramidites.

3.3. Desymmetrization via transition-metal-catalyzed intermolecular C–H functionalization

In addition to the intramolecular desymmetrization of tetrasubstituted organosilanes, the transition metal catalyzed intermolecular C–H functionalization of tetrasubstituted organosilanes is less mentioned in the literatures probably due to the difficulties to access the tetrasubstituted organosilanes bearing a directing group. Inspiring by the pyridine or pyrimidine directed C–H functionalizations of arylsilanes developed by Gevorgyan,[30] Xu and coworkers reported the first example of asymmetric desymmetrization of tetraorganosilanes via Pd-catalyzed azine-directed intermolecular C–H alkenylation (Scheme 18).[31] With chiral mono *N*-protected amino acid ligand (MPAA)[32] **L16** and pyridine as the directing group, the azine-tethered Si-stereogenic silanes were obtained in 37–71 % yields and 74–91 % ee. It is noteworthy that the replacement of



Scheme 17. Iridium-catalyzed asymmetric desymmetrization of diarylsilanols.



Scheme 18. Preparation of Si-stereogenic silanes via palladium-catalyzed intermolecular C–H olefination.

pyridine with quinoline led to better yields and enantioselectivities.

4. Conclusion

This Minireview summarizes the efficient construction of Si-stereogenic silanes via transition metal-catalyzed C–H activation approach. These methodologies are highly atom-economic and efficient thanks to the advances in C–H functionalization reactions, thus led to a wide range of silacycles, cyclic siloxanes, and heterocyclic attached tetraorganosilanes bearing a silicon-central chirality. The availability of novel silicon-containing structures has preliminarily facilitated the investigation of the physical properties and utility of Si-stereogenic compounds in organic synthesis and as optoelectronic materials.

Although elegant progress has been made in this field, the asymmetric synthesis of Si-stereogenic organosilane compounds is still in its infancy stage in comparison to the rapidly development of enantiochemistry of carbon center. The substrate scope of reported reactions is not broad enough, and the reaction patterns are largely limited to Rh- or Ir-catalyzed dehydrogenative C–H silylation, and Pd-catalyzed intramolecular C–H arylation. In order to accelerate greater progress in this underdeveloped research field, further developments include but not limited to the following directions: 1) the known processes are largely limited to the intramolecular C–H functionalization reactions, the intermolecular asymmetric C–H silylation of nondirected arenes or directing group enabled intermolecular both C(sp^2)–H and C(sp^3)–H functionalizations will enrich the structural and functional diversity of Si-stereogenic organosilane compounds; 2) the detailed mechanism investigations, including computational studies, toward the construction of silicon center chirality need to be explored, which will further facilitate the development of new reactions, more efficient catalysts or much broader reaction scope; 3) given the fact that high catalyst loading and precious metal catalysts are currently required in most cases, more efficient catalytic systems or cheaper abundant 3d metal catalysts are encouraged to be explored; 4) the applications of Si-stereogenic organosilane compounds in organic synthetic chemistry, material chemistry or medicinal chemistry will largely extend, along with the rapid development of efficient asymmetric reactions and the availability of structurally novel organosilane compounds. Undoubtably, development of efficient reactions for the preparation of Si-stereogenic organosilane compounds via transition metal-catalyzed C–H activation will be continuing as one of the most attractive and charming manner in light of the remarkable increase of attention in academia and industry.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Asymmetric · C–H Activation · Organosilanes · Si-stereogenic · Silylation

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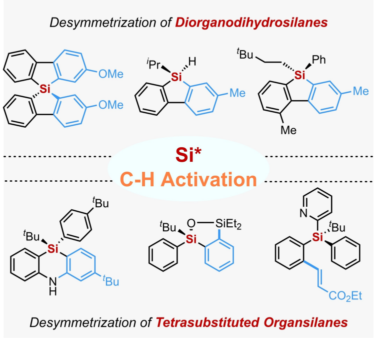
MINIREVIEWS

The preparation of chiral Si-stereogenic silanes, a class of functional molecules with increasing values in synthetic chemistry, medicinal chemistry, and material chemistry, via transition-metal-catalyzed C–H activation approach is an elegant and attractive manner, in short steps from simple starting materials. This Minireview summarizes the advances in construction of Si-stereogenic silanes by using this approach as well as future perspectives.



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Construction of Si-Stereogenic Silanes through C–H Activation Approach