CATALYTIC APPROACHES TO ACCESS CHIRAL SILACYCLIC COMPOUNDS

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Abstract. *Chiral silacyclic compounds are attracting increasing attention as they have promising applications in medicinal chemistry, material science and synthetic chemistry. As such, significant efforts have been made on the development of novel synthetic methodologies to access those molecules. This chapter provides a comprehensive summarization on the advances of catalytic construction via both transition metal catalysis and organocatalysis.*

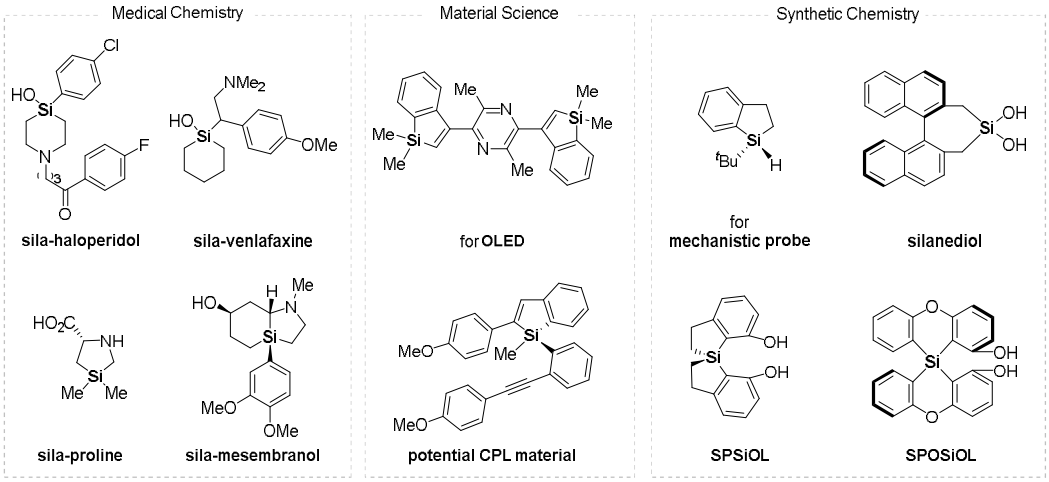
Contents

1. Introduction

Silacycles, cyclic frameworks with the replacement of at least one carbon atom by silicon, play an essential role in various areas, including medicinal chemistry and material science (Scheme 1).[1] Compared to the carbon atom, silicon features larger atomic radius, lower electronegativity and higher lipophilicity. Therefore, silacycles normally provides a more flexible conformation, which can significantly alter the bioactivity and photoelectron properties of functional molecules. The "carbon/silicon switch" strategy has therefore emerged as an attractive and efficient way in drug discovery for the development of new pharmaceutical candidates where silicon isosteres share similar behavior to their carbon analogues but with modified pharmacological properties and reduced toxicity.[2] Moreover, silacycles with π-conjugated system, such as siloles and their derivatives, have been employed as optoelectronic materials, which exhibit superior charge transport and luminescent properties for OLEDs and semiconductors.[3] Among them, chiral silacycles attract increasing attention as they have promising applications in medicinal chemistry, material science and synthetic chemistry.[4] For example, the incorporation of silicon-stereogenic centers enables advanced chiral materials for circularly polarized luminescence.[5] In synthetic chemistry, a Si-stereogenic cyclic monohydrosilane serves as mechanistic probe in transition metal catalyzed reactions.[4d] A recent representative application is the development of spirosilacycle-based chiral ligands. By leveraging the chiral spirosilacycle-based scaffold as the novel chiral platforms (*e. g.* **SPSiOL**, **SPOSiOL**), a series of chiral ligands bearing a large bite angle have been developed, which exhibit significant potential in asymmetric catalysis.[6]

Considering the importance of chiral silacycles, significant efforts have been made on the development of efficient synthetic methodologies for these molecules. However, the precise incorporation of silicon into chiral cyclic frameworks remains a longstanding challenge. For example, the construction of silicon-stereogenic centers is intrinsically difficult because of the presence of accessible 3d orbitals in silicon, which facilitates the formation of five- or six-coordinated intermediates that can undergo racemization or desilylation. Despite these difficulties, recent advances have enabled the synthesis of these structurally diverse

chiral molecules *via* the development of novel strategies. To date, a set of catalytic asymmetric reactions mediated by transition metal catalysis, including hydrosilylation, C–H silylation and [2+2+2]-cycloaddition, have been successfully applied to access these frameworks. More recently, organocatalytic approaches have also emerged as attractive alternatives for the preparation of chiral silacycles. In light of their importance and the rapid progress in this field, this chapter provides a comprehensive overview on the advances in catalytic approaches for the access of chiral silacyclic compounds.



Scheme 1. Applications of silacycles.

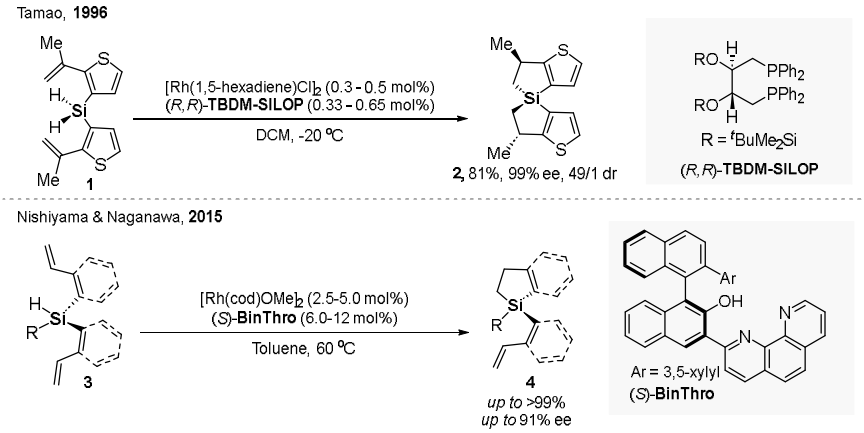
2. Construction of chiral silacycles *via* transition-metal catalysis

2.1. Construction of chiral silacycles *via* transition-metal catalyzed enantioselective hydrosilylation

Transition-metal catalyzed hydrosilylation has been considered as a fundamental and atom-economical protocol for the access of organosilicon compounds. The asymmetric variant was pioneered by the Ojima group, who developed a rhodium-catalyzed asymmetric hydrosilylation of α-keto esters.[7] Since then, numerous asymmetric hydrosilylation reactions of unsaturated substrates have been realized by employing suitable chiral ligands on the metal catalysts, enabling the access to a set of chiral organosilanes.[8] In 1996, this strategy was first applied to the construction of chiral silacycles by the Tamao group, where axially chiral thiophene-containing spirosilabiindane **2**, a potential building block for material science, was formed through rhodium-catalyzed intramolecular double hydrosilylation of styrene **1** using (*R,R*)-**TBDM-SILOP** as ligand (Scheme 2, top).[9] A few years later, Nishiyama and Naganawa realized a catalytic enantioselective desymmetrization of prochiral trisubstituted hydrosilanes **3**.[10a] By employing their axially chiral *N,N,O*-tridentate ligand (*S*)-**BinThro**,[10b] dihydrobenzosiloles **4** were obtained through intramolecular hydrosilylation of alkenes in good to high yields and up to 91 % ee (Scheme 2, bottom).

In 2020, Wang, Li and co-workers developed an efficient catalytic system for accessing chiral spirosilabiindane scaffolds *via* intramolecular double hydrosilylation of **5**.[6a] Notably, a pair of enantiomers **6**, **7** with excellent enantioselectivities and diastereoselectivities were obtained by employing either (*R,R*)-**Et-DuPhos** or (*R*)-**QuinoxP** as ligand (Scheme 3, top). Interestingly, **6a** could be obtained under the reported conditions in high efficiency with a low catalyst loading. Upon demethylation, enantiopure spirosilabiindane diol **SPSiOL** were accessible, which has been proven as a novel chiral scaffold for the development of a range of **SPSiOL**-based chiral ligands, including **SPSiP**, **SPSiPhos**, **SPSiPO** and **SPSiBox** ligands.[6] Two years later, the same group applied this strategy to the preparation of cyclic monohydrosilanes (Scheme 3, middle). The catalytic intramolecular hydrosilylation of **8** proceeded smoothly, affording a series of 5- and 6-membered silacycles **9** containing both carbon- and silicon-stereogenic centers with high diastereo- and enantioselectivities.[11] Most recently, the group reported the first catalytic kinetic resolution of monohydrosilanes for the construction of Si-stereogenic organosilanes (Scheme 3, bottom).[12] In this reaction,

both tetrasubstituted cyclic silanes **11** and monohydrosilanes (*R*)-**10** were formed in a single operation with excellent stereocontrol. (*S* factor up to 152).



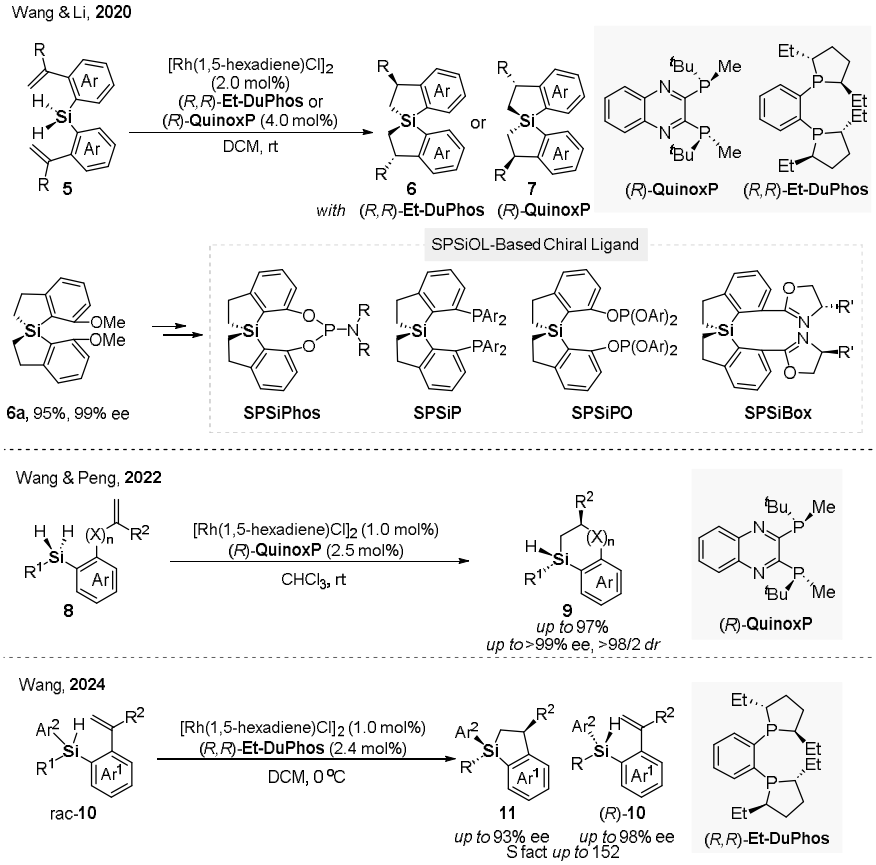
Scheme 2. Construction of chiral silacycles *via* Rh-catalyzed intramolecular hydrosilylation.

Catalytic intramolecular hydrosilylation normally requires the pre-synthesis of silicon-containing complex molecules as substrates. In 2022, the Meng group reported a Co-catalyzed cascade reaction between readily available 1,3-enynes **12** and monosubstituted silanes **13**, affording chiral cyclic alkenylsilanes containing both silicon- and carbon-stereogenic centers (Scheme 4, top).[13] With a combination of $Co(acac)_2$ and electron-deficient diphosphine ligand **L1**, the target cyclic silanes **14** were formed with good diastereo- and enantioselectivities. Mechanistically, this reaction proceeded through an intermolecular hydrosilylation of alkynes followed by Ojima-Crabtree isomerization and sequential intramolecular enantioselective hydrosilylation of alkenes. More recently, Xiong, Zhu and co-workers developed a Cu-catalyzed hydrosilylation of arylmethylenecyclopropanes **15** with **16** (Scheme 4, middle).[14] Employing axially hindered (*R*)-**DTBM-Segphos**, five-membered cyclic monohydrosilanes **17** with consecutive silicon- and carbon-stereogenic centers could be constructed with high diastereo- and enantioselectivities. Almost at the same time, the C. He and Ke group independently reported a similar transformation of **18** (Scheme 4, bottom).[15] In addition to the synthesis of cyclic monohydrosilanes **20** from monosubstituted silanes, this report also showcases the synthesis of chiral tetrasubstituted silacycles **19** by employing (*S*,*S*)-**Ph-BPE** as the chiral ligand.

Enantioselective hydrosilylation of C–C triple bond has also been involved in the construction of chiral silacycles. In 2020, the Xu group reported a Rh-catalyzed intramolecular *trans*-selective hydrosilylation of internal alkynes **21** by employing their developed Ar-BINMOL-Phos ligand **L2** (Scheme 5, top).[16] Mechanistic studies indicated that *P,O,O*-tridentate Ar-BINMOL-Phos were proposed to *in situ* form a stable mononuclear rhodium species in the presence of KO^{t}Bu, which is capable of affording the target silicon-stereogenic benzosiloles **22** in up to >98% ee. Moreover, the optical properties of these benzosiloles were investigated, revealing pronounced aggregation-induced emission (AIE) and circularly polarized luminescence (CPL) activities. Recently, the same group realized the first dynamic kinetic asymmetric transformations to construct Si-stereogenic centers (Scheme 5, bottom).[17] With their newly designed Ar-BINMOL-Phos phosphine-phosphoramidite ligand (**SiMOS-Phos**), silicon-stereogenic benzosiloles **24** were obtained in good enantioselectivities *via* a Rh-catalyzed intramolecular hydrosilylation of racemic alkynyl-tethered monohydrosilanes **23**.

Chiral heteroatom-containing silacycles can also be accessed *via* asymmetric hydrosilylation. In 2016, Shevlin, Chung and co-workers demonstrated a protocol for the synthesis of *N*-Boc-(*R*)-silaproline *via* Rh-catalyzed intramolecular hydrosilylation of **27**, which was synthesized *via* a *N*-alkylation of **25** with **26**. With this protocol, **28** was afforded with high enantioselectivities (>95% *ee*) in the presence of Josiphos-type ligand **L3** (Scheme 6, top).[18] Two years later, L.-W. Xu, Z. Xu and co-workers developed a Pt-catalyzed

tandem hydrosilylation/cyclization for the preparation of six-membered oxygen-containing silacycles. In this report, the enantioselective variant was preliminarily investigated between **29** and **30**, giving **31** in moderate yield and 32% ee using chiral diphosphine **L4** (Scheme 6, bottom).[19]

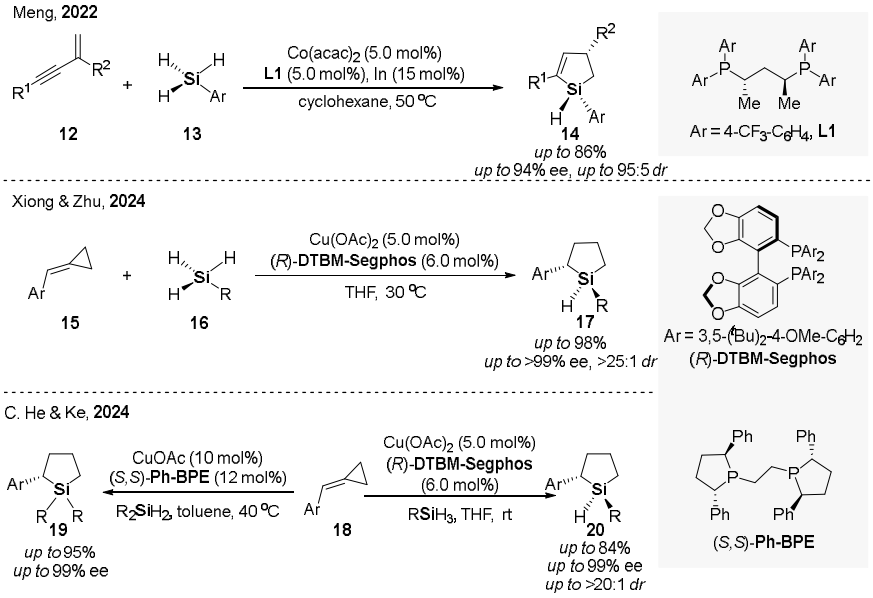


Scheme 3. Construction of chiral silacycles *via* Rh-catalyzed intramolecular hydrosilylation and their applications.

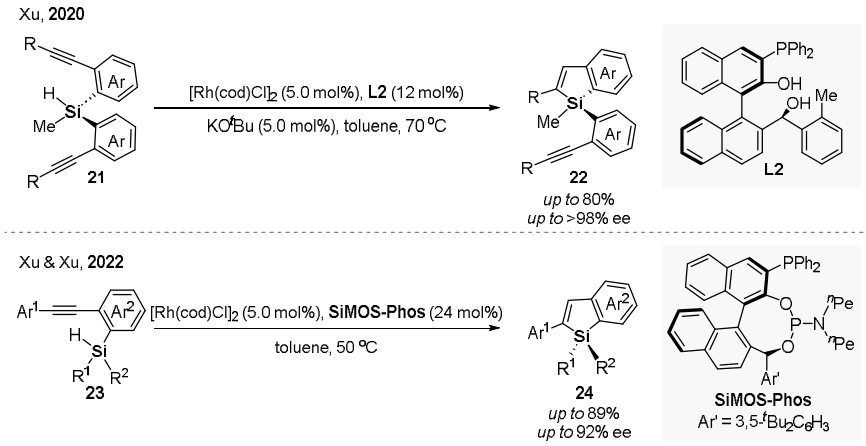
2.2. Construction of chiral silacycles *via* transition-metal catalyzed enantioselective C–H silylation

In 2013, Takai, Kuninobu and co-workers developed a protocol for the synthesis of chiral spirosilabifluorene derivatives **33**, valuable motifs in materials science. This intramolecular consecutive Csp^2–H silylation of **32** proceeded at 135 °C using [Rh(cod)Cl]$_2$/(*R*)-**BINAP** as catalyst, affording axially chiral spiro-9-silabifluorenes in up to 81% ee.[20a] Three years later, the same group revisited the reaction and a higher enantioselectivity (up to 95% ee) was achieved by lowering the reaction temperature (70 °C) (Scheme 7).[20b] Mechanistic studies indicated that the absolute configuration was determined in the first dehydrogenative silylation step, and a central- to axial-chirality conversion occurred in this process.

Taking into consideration the facile decomposition of monohydrosilanes with highly active transition-metal catalyst, the C. He group developed a cascade enantioselective intramolecular Csp^2–H silylation/intermolecular alkene hydrosilylation in 2020 (Scheme 8, top).[21] With this novel protocol, Si-stereogenic 9-silanfluorenes **37** or benzosilole-fused ferrocenes **38** were prepared using **34** or **35** as substrate and **36** as alkene source in the presence of [Rh(cod)Cl]$_2$ and chiral diphosphine ligand **L5** and (*R*)-**Segphos**.



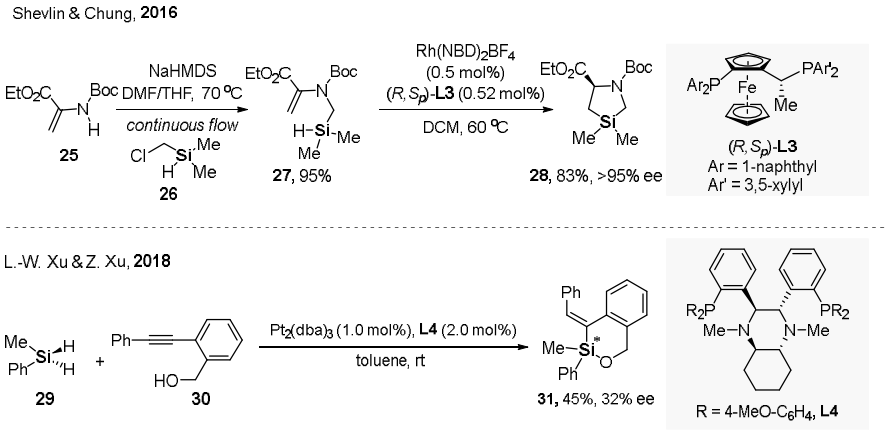
Scheme 4. Construction of chiral silacycles *via* cascade reactions.



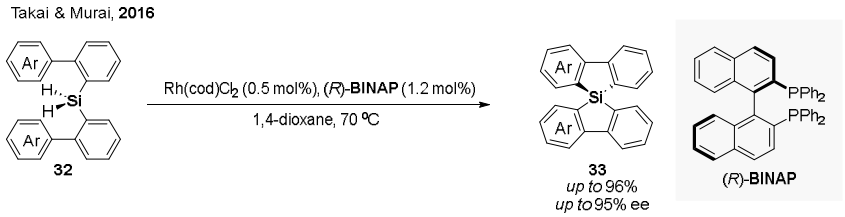
Scheme 5. Synthesis of Si-stereogenic benzosiloles *via* enantioselective hydrosilylation of C–C triple bond.

Shortly after, the W. He group reported the construction of five-membered chiral cyclic monohydrosilanes *via* Rh-catalyzed intramolecular Csp^2–H silylation of **39** or **40** (Scheme 8, above-middle).[22] By utilizing (*R*)-**DTBM-Segphos** as chiral ligand, a variety of silafluorenes **41** and benzosiloloferrocenes **42** were successfully obtained with excellent chemo- and enantioselectivities. Meantime, the C. He group demonstrated a related asymmetric synthesis of Si-stereogenic 1*H*-benzosiloles (Scheme 8, below-middle).[23] In this work, vinyldihydrosilanes **43** were employed as substrates to deliver cyclic monohydrosilanes **45** with excellent stereocontrol. Notably, the low catalyst loading (2.0 mol% of [Rh]) was crucial for the high efficiency. Moreover, metallocene-tethered dihydrosilanes **44** furnished 1*H*-benzosilolometallocenes **46** with both silicon-centered and planar chiralities with high diastereo- and enantioselectivities. With a careful substrate design, six- and seven-membered cyclic monohydrosilanes **49**, **50** have also been synthesized by the C. He group *via* Rh-catalyzed intramolecular Csp^2–H silylation of **47** or **48** by the employing a Josiphos-type

chiral diphosphine ligand **L5** or **L6** (Scheme 8, bottom).[24] The photophysical properties of those novel Si-stereogenic molecules were studies, displaying bright blue fluorescence, clear Cotton effects and CPL signals.



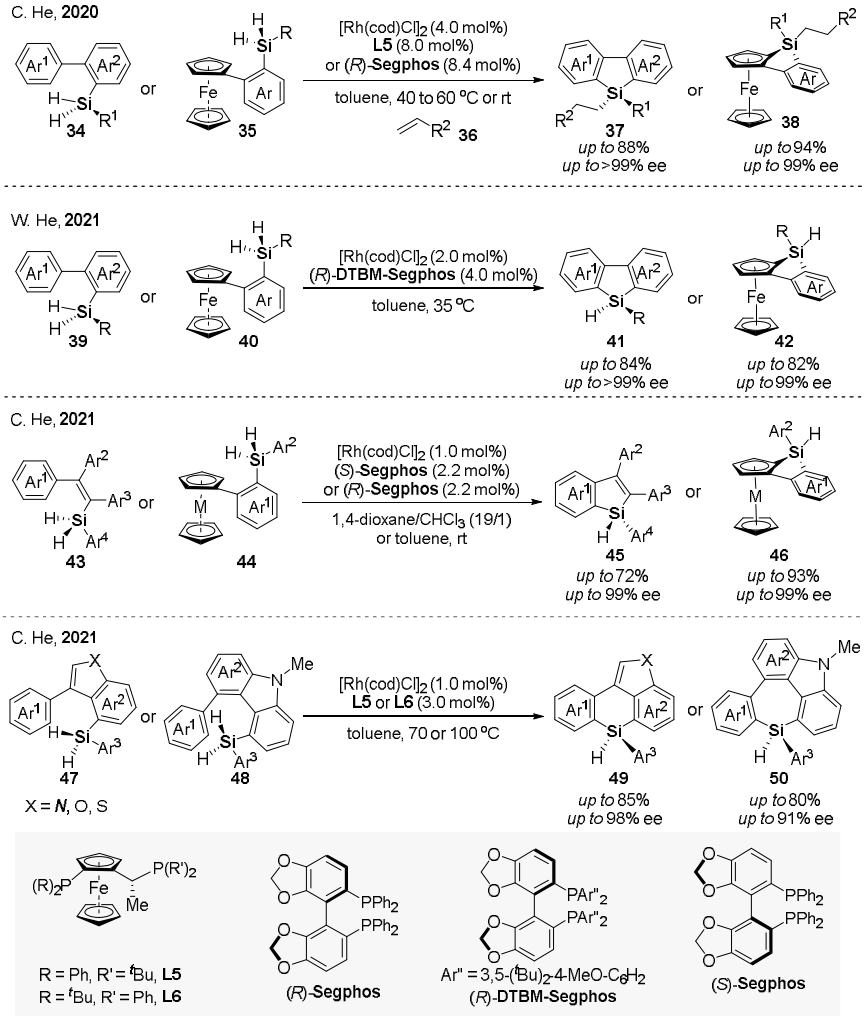
Scheme 6. Synthesis of heteroatom-containing chiral silacycles *via* asymmetric hydrosilylation.



Scheme 7. Synthesis of chiral spirosilabifluorene *via* intramolecular double C*sp*^{2}–H silylation.

In 2015, Takai, Murai and co-workers developed a ligand-accelerated Rh-catalytic intramolecular double C*sp*^{3}–H silylation, and later on they also demonstrated their effort on its enantioselective variant (Scheme 9, top).[25] However, only moderate chiral induction (40% ee) was achieved for axial-chiral 1,1'-spirosilabiindane **52** starting from substrate **51**. Later, the C. He group extended this strategy to the construction of Si-stereogenic dihydrobenzosiloles (Scheme 9, middle).[26] Again, to avoid the decomposition of monohydrosilanes, a cascade reaction involving Rh-catalyzed enantioselective C*sp*^{3}–H silylation/stereospecific alkene hydrosilylation was carried out using **53** and **54** as substrates, affording a series of enantioenriched **55** in up to 95% ee using (*R*,*S*$_p$)-Josiphos (**L5**) as chiral ligand. The same group later adapted this catalytic system to access six-membered Si-stereogenic dihydrodibenzosilines **57** (Scheme 9, bottom).[27] With the addition of the H_2 acceptor (NBE-OMe), compounds **57a-c** containing both central- and axial-chirality were obtained from **56** with high enantioselectivity, where a novel central-to-axial chirality relay was observed. Notably, the target chiral silacycles **57d-e** have also been achieved *via* kinetic resolution of dihydrosilanes bearing non-symmetric *ortho*-substituents on the aryl ring.

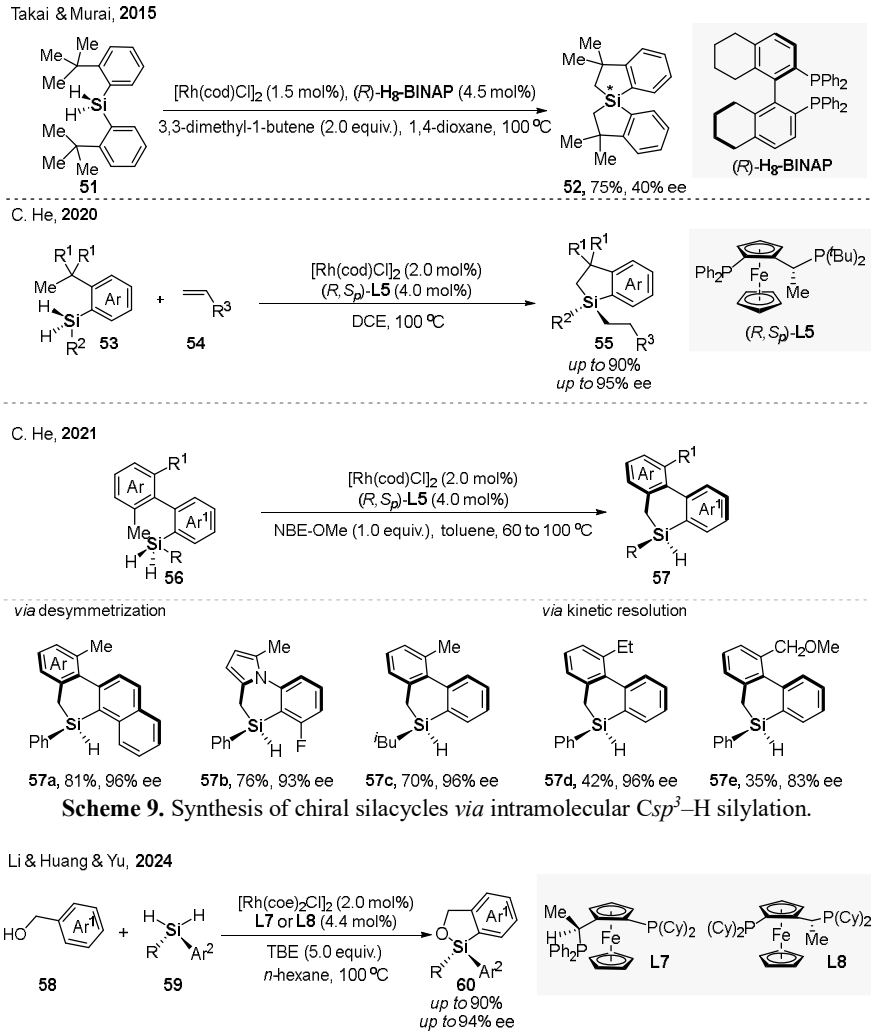
Recently, Li, Huang, Yu and co-workers reported the construction of Si-stereogenic oxasilacycles (Scheme 10).[28] A cascade reaction involving an intermolecular O–H silylation and sequential intramolecular C–H silylation using benzyl alcohols **58** and dihydrosilanes **59** as substrates delivered a set of cyclic silyl ethers **60** efficiently in up to 94% ee. Notably, a single catalytic system (Rh/Josiphos-type ligand **L7** or **L8** was sufficient to promote both dehydrogenative silylation steps. Mechanistic studies indicated that the O–H silylation was the enantio-determining step and the sequential C–H silylation proceeded in a stereospecific manner.



Scheme 8. Synthesis of Si-stereogenic silacycles *via* intramolecular Csp^2–H silylation.

The C–H silylation strategy has also been employed for construction of silacycles with multiple chiralities. Inspired by the Hartwig group's breakthrough in catalytic C–H silylation,[29] the W. He group developed a Rh-catalyzed enantioselective Csp^2–H silylation of **61**, enabling the synthesis of planar-chiral metallocene siloles in 2015 (Scheme 11, top).[30] After carefully screening chiral ligands, the sterically hindered (*S*)-**TMS-Segphos** was identified as the most effective, allowing the reaction performed under mild conditions (rt to 45 °C). Moreover, the steric hindrance of substituents on silicon atom significantly affected both efficiency and chiral induction of the reaction, and 97% ee was reached with a ^{n}Pr substituent **62b**. Shortly after, Takai, Murai and co-workers demonstrated a similar catalytic system for accessing metallocene-fused benzosiloles with planar chirality (Scheme 11, above-middle).[31] In this work, (*R*)-**DTBM-Segphos** was employed as the optimal chiral ligand, delivering the target enantioenriched silacycles **62e-h** in up to 93% ee. Meantime, an alternative chiral catalyst system was reported by the Sasaki and Shibata group for obtaining planar-chiral benzosililoloferrocenes in good yields and up to 86% ee (Scheme 11, below-middle).[32] The reaction proceeded smoothly with the combination of $[Rh(coe)Cl]_2$ and chiral diene **L9**. Notably, the hydrogen acceptor **63** was required for better efficiency and enantioselectivity. A few years later, the Zhao group

developed a novel protocol for accessing six-membered π-conjugated dibenzooxasilines *via* C*sp*^{2}–H silylation of **64** (Scheme 11, bottom).[33] This Rh-catalyzed 2-arylphenol derived process could also occur in an enantioselective manner. With chiral Josiphos **L8** as the ligand and cyclohexene as the hydrogen acceptor, various ferrocene-fused benzooxasilolines **65** bearing planar chirality were obtained in up to 95% ee.

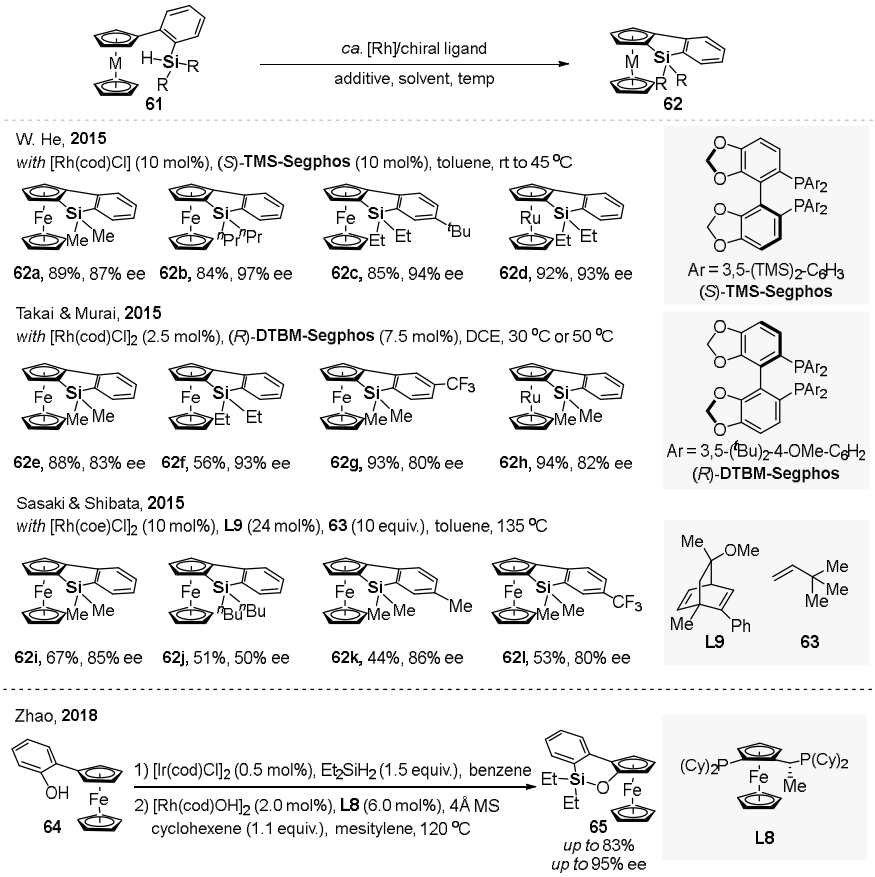


Scheme 9. Synthesis of chiral silacycles *via* intramolecular C*sp*^{3}–H silylation.

Scheme 10. Synthesis of Si-stereogenic oxasilacycles *via* intermolecular O–H silylation/intramolecular C–H silylation.

In 2015, Hartwig, Ryberg and co-workers reported a Rh-catalyzed enantioselective C*sp*^{2}–H silylation for the synthesis of C-stereogenic oxygen-containing silacycles (Scheme 12, top).[34a] In this reaction, (hydrido)silyl ethers **66**, *in-situ* generated *via* Ir-catalyzed intermolecular hydrosilylation of benzophenone derivatives, underwent enantioselective intramolecular C–H silylation to deliver **67a-c** in high yields and excellent enantioselectivities, using norbornene as the H_2 acceptor. Notably, various chiral diphosphite ligands were evaluated, and catASium-type **L10** and **L11** and Walphos-type **L12** ligands were found to be most effective. Mechanistic studies indicated that C–H bond cleavage along with C–Si bond formation affected the

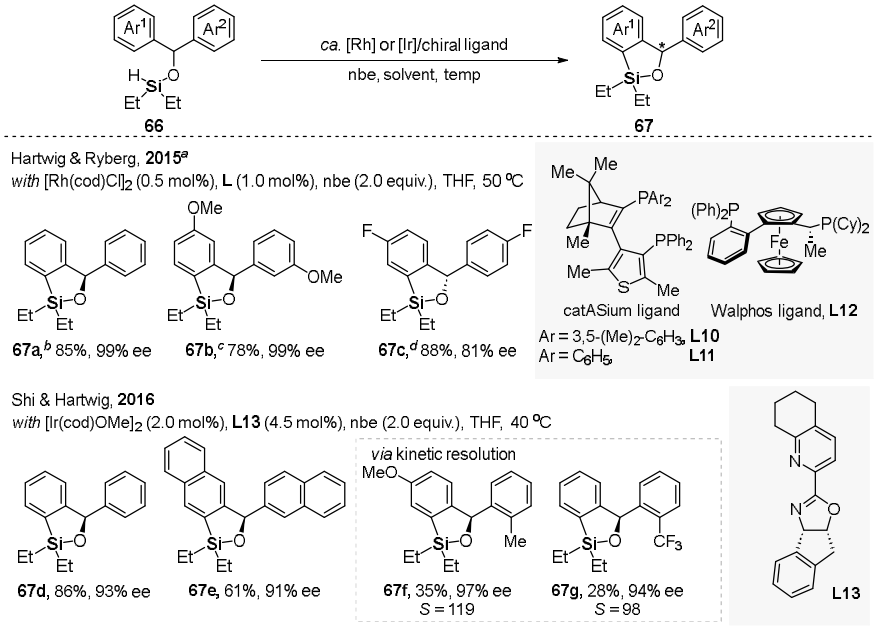
chiral induction.[34b] Next year, Shi, Hartwig and co-workers revisited this reaction, and developed a new catalytic system (Ir/pyridinyloxazoline) (Scheme 12, bottom).[35] By utilizing chiral dinitrogen ligand **L13**, desymmetrization of symmetrical diarylmethyl silanes proceeded smoothly to afford chiral oxygen-containing silacycles **67d-e** with high regioselectivities. Moreover, **67f-g** were prepared under similar reaction conditions *via* a kinetic resolution strategy with excellent stereoselectivities (up to 97% ee and *S* factor up to 119).



Scheme 11. Synthesis of silacycles with planar chirality.

In 2015, Takai, Murai and co-workers attempted to achieve the enantioselective variant for their Rh-catalytic intramolecular C*sp*^{3}–H silylation of **68**. However, an insufficient chiral induction was observed in the target product **69** after evaluation of chiral ligands (Scheme 13, top).[25] The next year, the Hartwig group reported their achievement in the synthesis of cyclopropane-fused oxygen-containing silacycles *via* enantioselective intramolecular C*sp*^{3}–H silylation (Scheme 13, above-middle).[36] Considering the high reactivity of C*sp*^{3}–H bond of cyclopropane and the rigid conformation, silyl ethers **71** were designed as the substrates, which were obtained by a Ru-catalyzed intermolecular hydrosilylation of **70**. A set of enantioenriched **72** were then delivered with the combination of $[Rh(cod)Cl]_2$ and (*S*)-**DTBM-Segphos** using cyclohexene as the H_2 acceptor. Notably, both the bulkiness of chiral ligand and the H_2 acceptor were crucial for the high efficiency and enantioselectivity. The next year, the same group reported an Ir-catalyzed enantioselective intramolecular primary C*sp*^{3}–H silylation for preparing dihydrobenzosiloles (Scheme 13, below-middle).[37] Using the established catalytic system for C*sp*^{2}–H silylation (Scheme 12), desymmetrization of isopropyl groups in **73** proceeded efficiently to deliver **74** in up to 96% ee. Moreover, the utility of this

methodology was demonstrated by the late-stage functionalization of a biologically active dehydroabietic acid derivative **75**. Chiral cyclic **77** was obtained in good yield and high diastereoselectivity under the optimal conditions via Csp^2–H silylation of **76**, which was prepared through the installation of dimethylsilyl group from **75**. They also extended this strategy to the synthesis of azasilacycles, silicon-based analogs of azacycles, which is a privileged scaffold found in many bioactive molecules and pharmaceuticals.[38] The enantioselective variant has been realized by the utilization of more electron-rich pyridyl imidazoline ligand **L14**/Ir catalyst system, and **78** as substrate, affording several silapyrrolidines **79** in good yields and up to 83% ee (Scheme 13, bottom).



[a] Yield of two steps where **66** was formed in situ from benzophenone derivatives. [b] with **L10**. [c] with **L11**. [d] with **L12**.

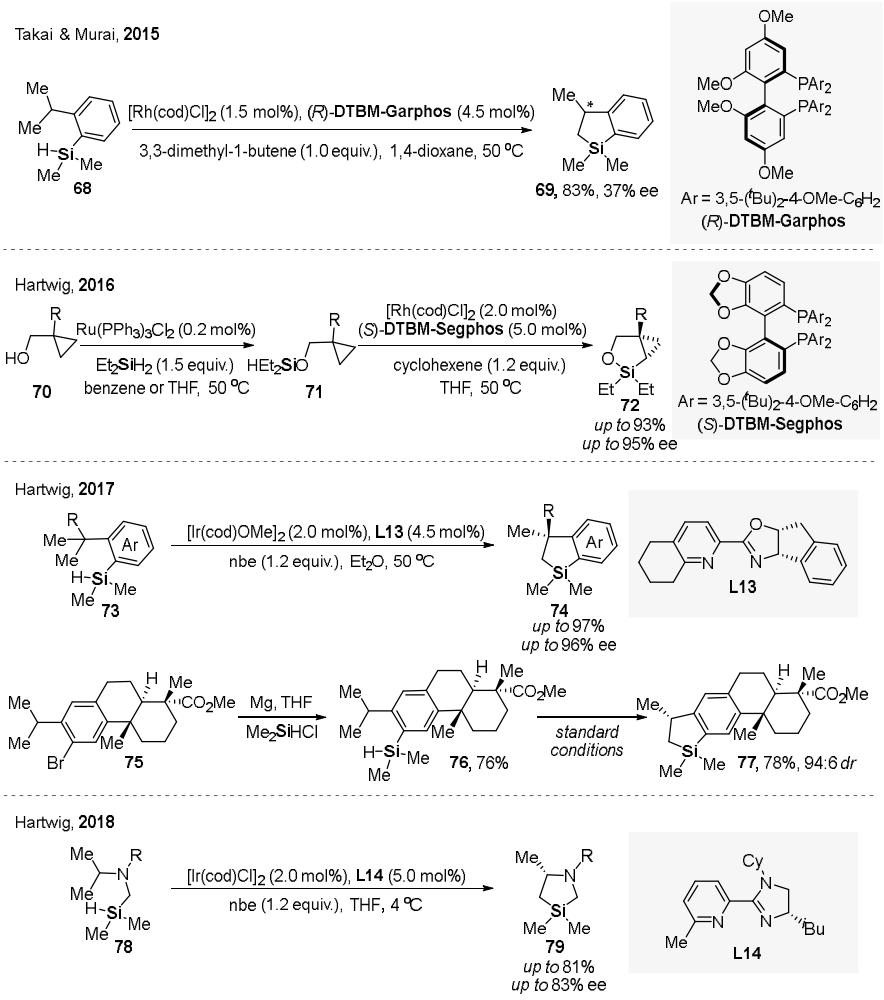
Scheme 12. Synthesis of C-stereogenic silacycles *via* enantioselective Csp^2–H silylation.

2.3. Construction of chiral silacycles *via* transition-metal catalyzed C–Si bond activation process

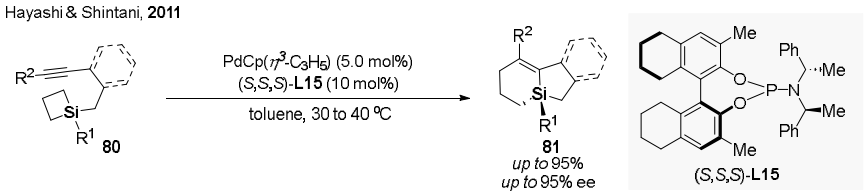
SCBs (silacyclobutanes) and their derivatives, characterized by their strained silacyclic frameworks, are valuable precursors for constructing silacycles *via* C–Si bond activation. The initial research on this field was reported by Imai and Sakurai in 1970s, in which SCBs reacted with electron-deficient alkynes under Pd catalysis.[39] Until 2011, the first asymmetric version was realized by Hayashi, Shintani and co-workers.[40] They designed alkyne-tethered SCBs **80** as substrate, enabling the Pd-catalyzed intramolecular ring-expansion. Using a sterically hindered H_8-BINOL-derived phosphoramidite ligand **L15**, Si-stereogenic cyclic tetraorganosilicons **81** were obtained with high chemo- and enantioselectivities (Scheme 14).

A year later, Hayashi, Shintani and co-workers reported a Pd-catalyzed intermolecular cycloaddition of SCB **82** with electron-deficient alkynes **83** by utilizing the same catalyst system (Scheme 15, top).[41] Various Si-stereogenic 1-sila-2-cyclohexenes **84a-d** were obtained in up to 94% ee. Notably, unsymmetrical alkyne underwent smoothly to reach **84c** exclusively. However, for terminal alkenes, cycloaddition product **84d** was obtained with moderate enantioselectivity (77% ee). In 2019, the Song group developed a Rh-catalytic system, enabling the use of unactivated terminal alkynes as substrates (Scheme 15, bottom).[42] By employing $[Rh(CH_2{=}CH_2)_2Cl]_2$ and BINOL-derived phosphoramidite ligand **L16**, a set of silacyclohexenes **84e-h** bearing Si-stereogenic center were constructed with high chemo- and enantioselectivities (up to 82% ee). This methodology was later applied as a key step to the synthesis of (−)-sila-mesembranol, which exhibits enhanced

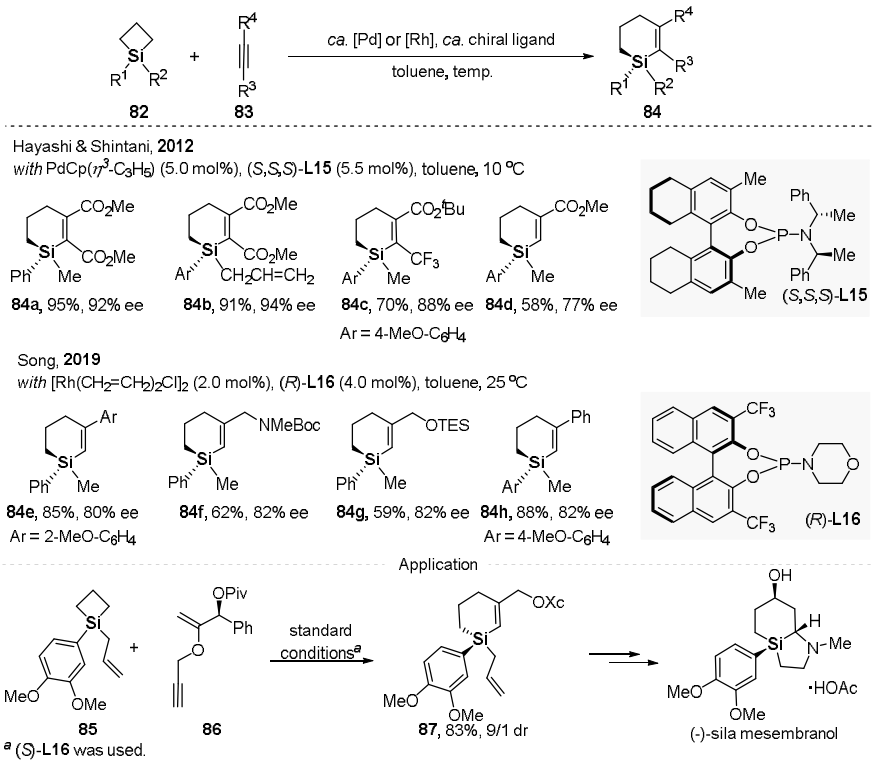
antidepressant effects compared to its natural carbon analog (–)-mesembranol in murine models.[4g] As shown in Scheme 15, SCB derivative **85** reacted with **86** to deliver **87** in 83% yield, which could be further transformed to (–)-sila-mesembranol.



Scheme 13. Synthesis of C-stereogenic silacycles *via* enantioselective Csp^3–H silylation.



Scheme 14. Synthesis of Si-stereogenic silacycles *via* a Pd-catalyzed intramolecular cycloaddition of SCB with alkynes.

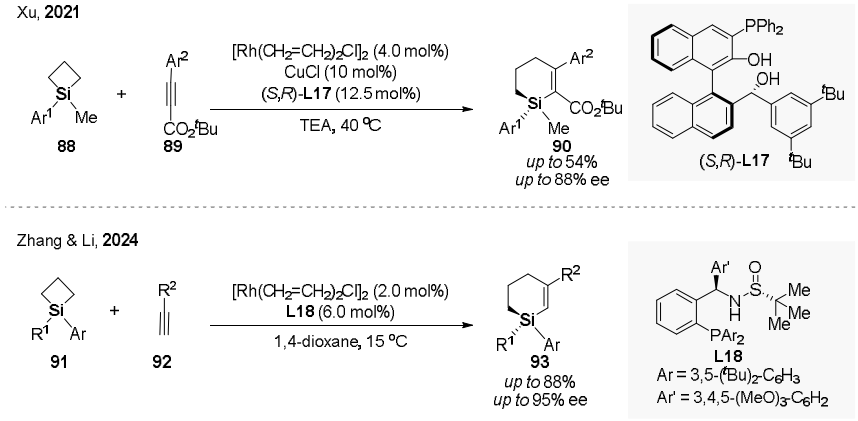


Scheme 15. Synthesis of Si-stereogenic silacycles *via* an intermolecular ring-expansion reaction of SCB with alkynes.

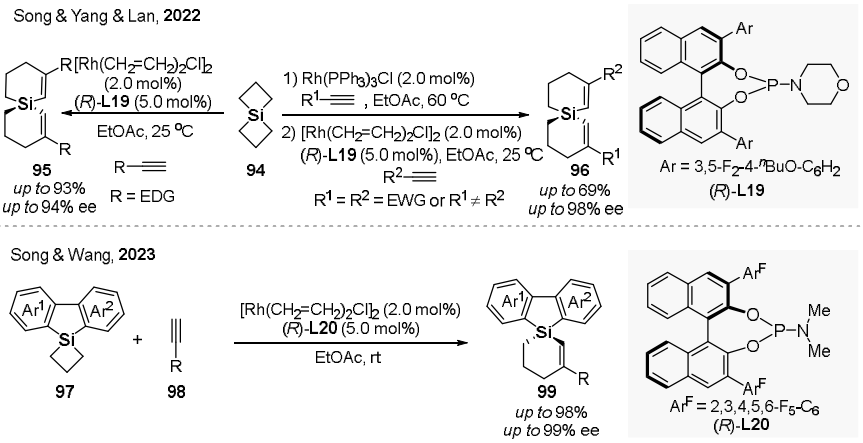
In 2021, the Xu group reported a bimetallic Rh/Cu-based catalytic system for the synthesis of six-membered silacycles (Scheme 16, above).[43] In this work, a series of newly developed Ar-BINMOL-Phos were tested using **88** and internal electron-deficient alkynes **89**, delivering the target products **90** in up to 88% ee. In 2024, Zhang, Li and co-workers further improved the enantioselectivity of this reaction by employing chiral sulfinamide phosphine ligand **L18** (Scheme 16, bottom).[44] In this study, SCBs **91** reacted with more challenging terminal alkynes **92** in the presence of $[Rh(CH_2{=}CH_2)_2Cl]_2$, affording the Si-stereogenic silacyclohexenes **93** with excellent enantioselectivities (up to 95% ee).

Apart from the construction of central chirality, Song, Yang, Lan and co-workers reported a Rh-catalyzed asymmetric dual ring expansion of **94** for the access of axial-chiral spirosilabicyclohexenes in 2022 (Scheme 17, top).[45] For electron-rich alkynes, chiral 6/6-silaspiranes **95** were prepared efficiently with high enantioselectivities using a sterically demanding BINOL-derived phosphoramidite ligand **L19**. In contrast, when electron-deficient alkynes were employed, the reaction required a two-step process due to the catalyst deactivation after the first ring expansion. This two-step process was further applied to the access of hetero-disubstituted spirosilabicyclohexenes **96** from two different alkynes. In the following year, the same group reported the enantioselective synthesis of 6/5-Spirosilafluorenes (Scheme 17, bottom).[46] Using a similar catalytic system, silacyclobutane-spirofused **97** reacted with terminal alkynes **98** through the ring expansion reaction, producing **99** with excellent chiral induction (up to 99% ee).

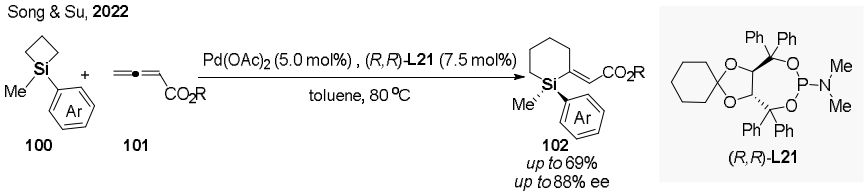
The ring expansion of SCBs could also be realized using allenes as the substrates. In 2022, Song, Su and co-workers developed a methodology for the synthesis of 2- or 3-(*E*)-enoate-substituted silacyclohexenes.[47] The use of $Pd(OAc)_2$ and a TADDOL-derived ligand allowed the cycloaddition of SCBs **100** with allenoates **101**, affording Si-stereogenic **102** with excellent regioselectivity and good enantioselectivity (Scheme 18).



Scheme 16. Synthesis of Si-stereogenic silacycles *via* an intermolecular cycloaddition of SCB with alkynes.



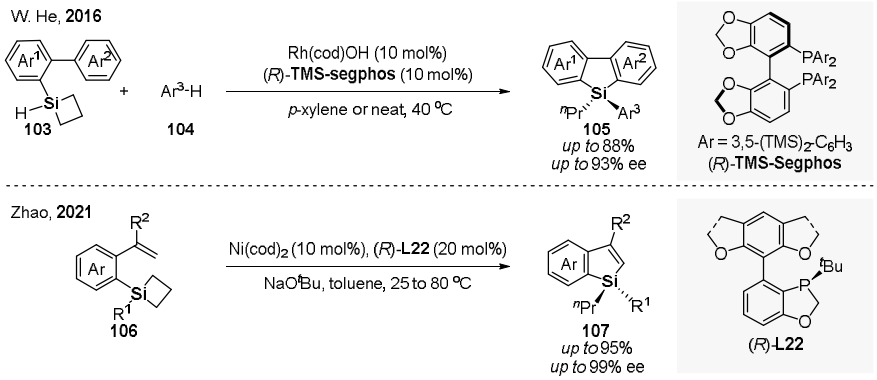
Scheme 17. Synthesis of axial-chiral silacycles *via* cycloaddition of SCB with alkynes.



Scheme 18. Synthesis of chiral silacycles *via* cycloaddition of SCB with allenes.

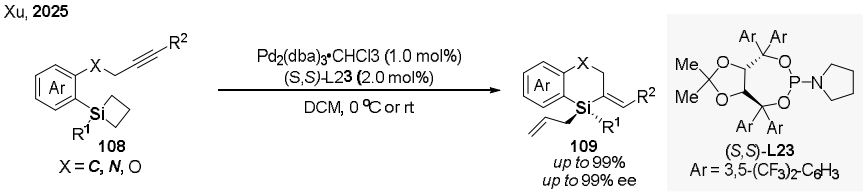
In addition to ring-expansion reactions, ring-opening reactions of SCBs have also been applied to the construction of chiral silacycles. Initial studies were explored by the W. He group in 2016 where a Rh-catalyzed asymmetric tandem SCBs ring opening/intermolecular Csp^2–H silylation reactions were developed (Scheme 19, top).[48] The reaction between SCBs **103** and (hetero)arenes **104** was performed in the presence of Rh(cod)OH and (*R*)-**TMS-Segphos**, delivering Si-stereogenic dibenzosiloles **105** regioselectively in up to 93% ee. In 2021, the Zhao group realized the first Ni-catalyzed ring-opening process of SCBs (Scheme 19, bottom).[49] Employing a P-chiral monophosphorus ligand (*R*)-**L22** developed by Tang's group,[50]

2-alkenylaryl-tethered SCBs **106** efficiently provided Si-stereogenic benzosiloles **107** with high enantioselectivities (up to 99% ee) *via* a ring opening/intramolecular Csp^2–H silylation sequence.



Scheme 19. Synthesis of chiral silacycles *via* tandem SCBs ring-opening/intermolecular Csp^2–H silylation.

Recently, the Xu group developed an asymmetric intramolecular ring-opening reaction of SCBs with alkynes, which is normally the side reaction in previous studies (Scheme 20).[51] Alkyne-tethered SCBs **108** were used as substrates to afford six-membered Si-stereogenic benzofused silacycles **109** with precise regioselective control. The employment of TADDOL-derived phosphoramidite ligand **L23** facilitated the excellent chiral induction.



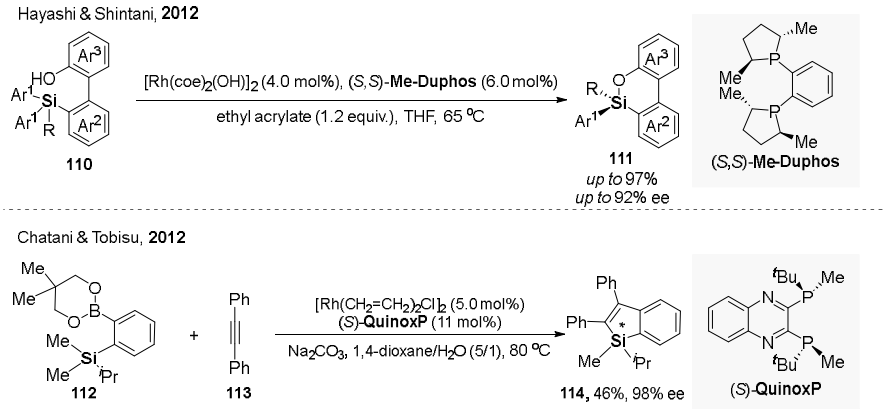
Scheme 20. Synthesis of chiral silacycles *via* tandem SCBs intramolecular ring-opening/silacyclization.

Desymmetrization of prochiral acyclic tetraorganosilanes *via* catalytic C–Si activation is another approach for the construction of chiral silacycles. In 2012, Hayashi, Shintani and co-workers demonstrated a synthetic protocol for the access of Si-stereogenic dibenzooxasilines (Scheme 21, top).[52] Hydroxy-tethered diarylsilanes **110** underwent enantiodiscriminating transmetalation to give six-membered **111** in the presence of Rh/(*S,S*)-**Me-Duphos**. Notably, ethyl acrylate was crucial to regenerating the active catalytic species. Shortly after, Chatani, Tobisu and co-workers developed a Rh-catalyzed C–Si activation, in which 2-trimethylsilylphenylboronic acid **112** reacted with internal alkynes **113** to afford benzosiloles.[53] The enantioselective version was realized with (*S*)-**QuinoxP** as the ligand, affording benzosiloles **114** in 98% ee (Scheme 21, bottom).

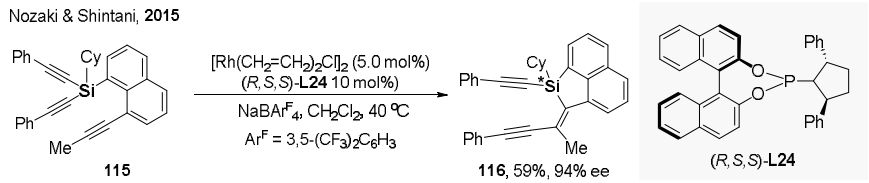
In 2015, Nozaki, Shintani and co-workers reported a catalytic intramolecular alkynylsilylation of alkynes to afford six-membered silacycles *via* C*sp*–Si bond cleavage.[54] The enantioselective variant was also explored using 8-alkynylnaphthene-tethered dialkynylsilane **115** as the substrate, giving the corresponding product **116** in 59% yield and 94% ee in the presence of BINOL-derived phosphoramidite **L24** (Scheme 22).

Meantime, the Ogoshi group demonstrated a Ni-catalyzed asymmetric synthesis of benzoxasiloles.[55] By employing chiral NHC ligand **L25**, an intramolecular aryl transfer process took place with the facilitation by the coordination pattern of the Ni-NHC complex to the substrate, affording enantioenriched **119** with high enantioselectivities from **117** (Scheme 23, top). When two aryl groups attached on the silicon atom **118**, **120** were formed containing both carbon- and silicon-stereogenic centers. Recently, an alternative protocol for the enantioselective synthesis of benzoxasiloles has been developed by L.-W. Xu, Z. Xu, Cao and co-workers

(Scheme 23, bottom).[56] The Si–O coupling of [2-(hydroxymethyl)phenyl]silanes **121** was achieved to produce **122** *via* Cu-mediated transmetalation of pentacoordinated silicate species with high enantioselectivities using Segphos-type chiral ligand **L26**. Moreover, carbon- and silicon-stereogenic silacycles **123** were also constructed *via* kinetic resolution strategy in the presence of PyrOx ligand **L27**.



Scheme 21. Synthesis of chiral silacycles *via* catalytic C–Si activation.



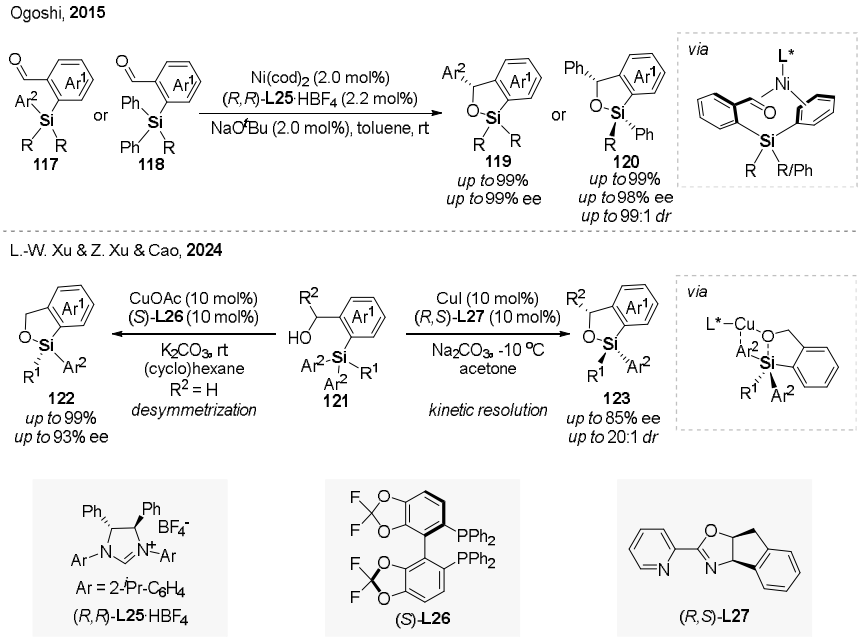
Scheme 22. Synthesis of chiral silacycles *via* intramolecular alkynylsilylation of alkynes.

Recently, the preparation of 4-sila-4*H*-benzo[*d*][1,3]oxazines **125** has been developed by the Shintani group *via* an intramolecular Hiyama coupling reaction with **124**.[57] By introducing Josiphos-type ligand **L28**, good chiral induction was achieved for this reaction (Scheme 24). The mechanistic studies revealed that an intramolecular transmetalation *via* inversion at silicon was involved during the reaction.

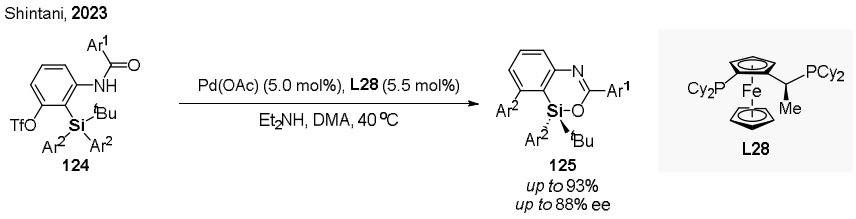
Silacycles with other chiral elements have also been accessed *via* asymmetric C–Si cleavage. In 2020, the Xu group developed a palladium catalyzed reaction between benzosilacyclobutanes **126** and cyclopropenes **127**, enabling the diastereoselective synthesis of silabicyclo[4.1.0]heptanes with a high-strained bicyclic skeleton.[58] The asymmetric variant was also demonstrated using TADDOL-derived phosphoramidite **L29**, affording the target silacycles **128** containing three consecutive carbon stereocenters (Scheme 25, top). Recently, Song, Lan and co-workers demonstrated a ligand-controlled regiodivergent intermolecular ring expansion of benzosilacyclobutenes **129** with internal alkynes **130** for the access of axially chiral silacycles (Scheme 25, middle).[57] The selectivity of Csp^2–H versus Csp^3–H bond cleavage in benzosilacyclobutene was governed by the ligand cavity size. The use of H_8-BINOL-derived phosphoramidite **L30** with a cavity size of 9.5 Å promoted Csp^3–H bond activation to deliver **131** with high enantioselectivities (up to 98% ee), whereas a SPINOL-based phosphoramidite **L31** with a small catalytic pocket (cavity size of 5.7 Å) favored Csp^2–H bond cleavage to give **132** in up to 96% ee. In the same year, Li, Wang and co-workers reported the synthesis of enantioenriched seven-membered silacycles.[60] A Rh-catalyzed asymmetric [4+3]-annulations between benzosilacyclobutenes **133** and 7-oxabenzonorbornadienes **134** furnished a series of medium-sized silacycles **135** with excellent enantio-induction in the presence of (*S*)-**QuinoxP** (Scheme 25, bottom).

In 2021, Wang, Lan and co-workers developed a Pd-catalyzed enantioselective carbene insertion reaction of **136** for the synthesis of carbon-stereogenic five-membered silacycles **138** (Scheme 26, top).[61] Using trisylhydrazones **137** as the carbene precursors and BINOL-derived phosphoramidite **L32** as the optimal

ligand, the enantioselective carbene insertion reaction with SCBs led to **138** with excellent chiral induction. Notably, cyclic trisylhydrazones were also suitable substrates, giving the corresponding chiral spiro silanes. In the following year, they further extended this strategy to the access of benzo-fused silacycles **141** (Scheme 26, bottom).[62] The reaction between benzosilacyclobutanes **139** and **140** proceeded smoothly under the similar conditions, achieving excellent site- and enantioselectivities with the sterically hindered **L32** favoring Csp^3–Si bond cleavage.



Scheme 23. Synthesis of chiral benzoxasiloles *via* an intramolecular aryl transfer process.

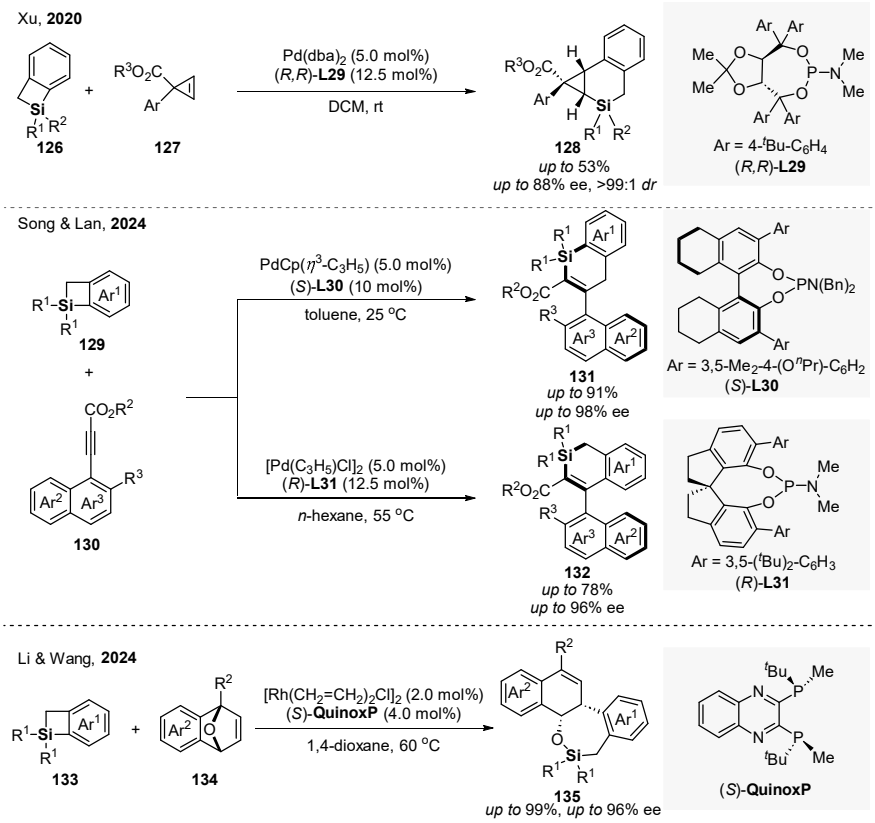


Scheme 24. Synthesis of 4-sila-4*H*-benzo[*d*][1,3]oxazines *via* intramolecular Hiyama coupling reaction.

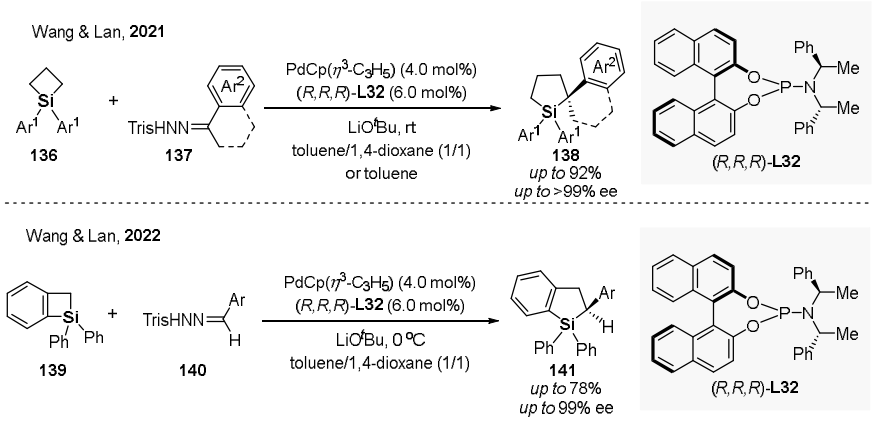
2.4. Construction of chiral silacycles *via* transition-metal catalyzed enantioselective [2+2+2]-cycloaddition

Nozaki, Shintani and co-workers developed a series of enantioselective [2+2+2]-cycloaddition for the construction of Si-stereogenic organosilanes. In 2015, silicon-containing prochiral triynes **142** were designed for this [2+2+2]-cycloaddition with internal alkynes **143** (Scheme 27, top).[63] A set of Si-stereogenic dibenzosiloles **144** were obtained in up to 96% ee by employing an axially chiral monophosphine ligand **L33**. Shortly after, the same type of prochiral triynes **145** were reacted with isocyanate **146** under identical reaction conditions, delivering heterocycle-fused dihydrobenzosilolopyridinones **147** with high regioselectivities and enantioselectivities (Scheme 27, middle).[5c] In 2020, the same group further explored the access of six-membered silacycles *via* the same approach.[5e] In this case, the asymmetric [2+2+2]-cycloaddition

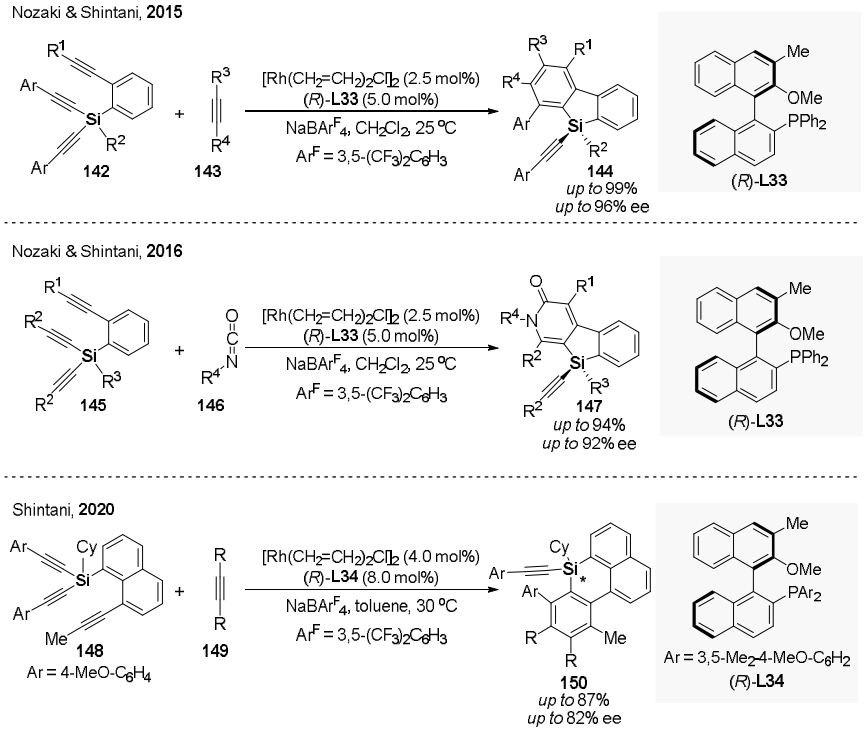
8-alkynylnaphthene-tethered dialkynylsilanes **148** with alkynes **149** produced 7*H*-benzo[*e*]naphtho[1,8-*bc*]silines **150** in up to 82% ee using chiral monophosphine (*R*)-**L34** (Scheme 27, bottom).



Scheme 25. Synthesis of silacycles with other chiralities *via* asymmetric C–Si cleavage.

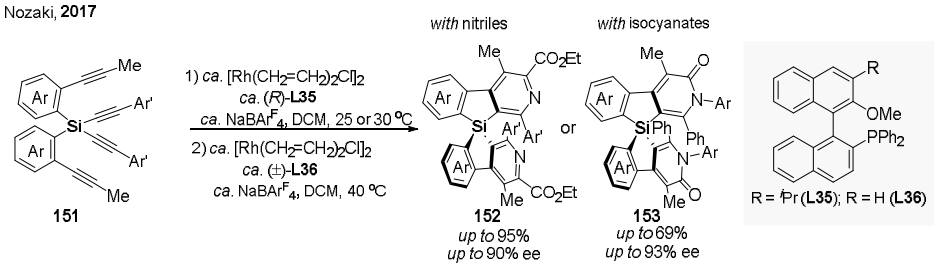


Scheme 26. Synthesis of chiral silacycles *via* carbene insertion.



Scheme 27. Synthesis of Si-stereogenic silacycles *via* [2+2+2]-cycloaddition.

The same authors also applied the [2+2+2]-cycloaddition approach to afford spirosilacycles with axial chirality (Scheme 28).[5d] The reaction of tetraynes **151** with nitriles or isocyanates enabled by a combination of monophosphine (*R*)-**L35**/$[Rh(CH_2{=}CH_2)_2Cl]_2$ followed by the addition of Rh/(±)-**L36**, delivering the chiral spirocyclic compounds **152** or **153** in up to 93% *ee*.

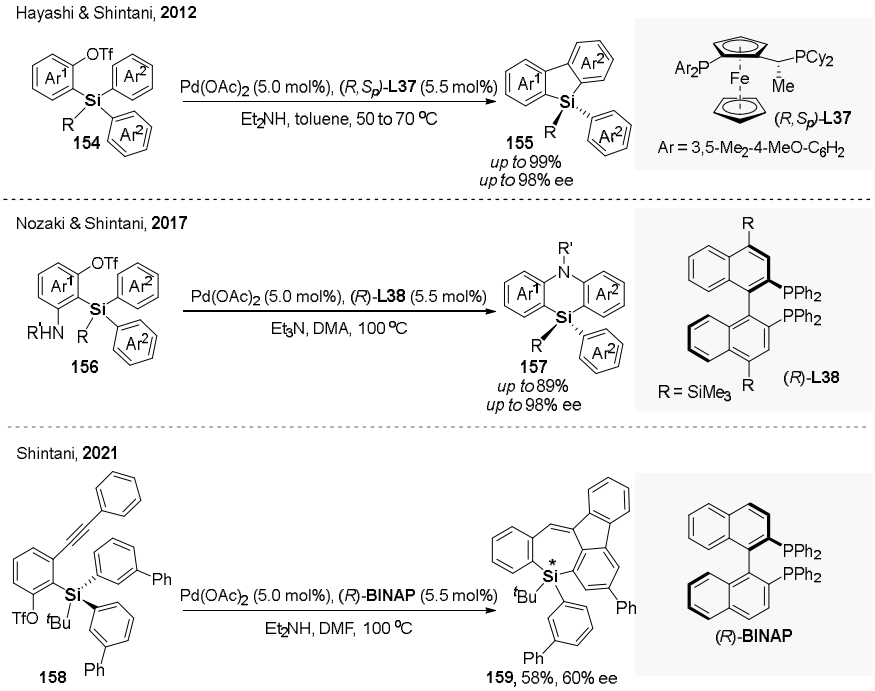


Scheme 28. Synthesis of axial-chiral silacycles *via* [2+2+2]-cycloaddition.

2.5. Construction of chiral silacycles *via* other transition-metal catalytic approaches

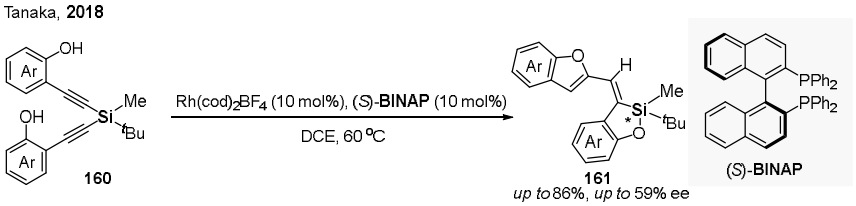
In 2012, the Hayashi and Shintani group developed a Pd-catalyzed asymmetric intramolecular C–H arylation reaction of prochiral 2-(diarylsilyl)aryl triflates **154** (Scheme 29, top).[64] Si-stereogenic dibenzosiloles **155** were constructed with high enantioselectivities by a combination of $Pd(OAc)_2$ and Josiphos-type ligand **L37**. When 3-amino-substituted (arylsilyl)aryl triflates **156** were used, Si-stereogenic 5,10-dihydrophenazasilines **157** were produced, and the best chiral induction was obtained using chiral bis(trimethylsilyl)-substituted BINAP **L38** (Scheme 29, middle).[65] Mechanistic studies indicated that a

1,5-palladium migration was the enantio-determining step. Subsequently, 1,n-palladium migration was applied to constructing other complicate silacycles in one single operation.[66] For instance, 3-alkyne-substituted (arylsilyl)aryl triflates were employed to produce 5*H*-dibenzo-[*b*,*f*]silepins efficiently through a series of 1,n-palladium migrations and an unconventional *anti*-carbopalladation step with alkynes. Using (*R*)-**BINAP** as the chiral ligand and **158** as substrate, this Pd-catalyzed reaction offered an enantioselective way to the preparation of **159** with a promising enantioselectivity (Scheme 29, bottom).



Scheme 29. Synthesis of Si-stereogenic silacycles *via* intramolecular C–H arylation reaction and 1,n-Pd migration.

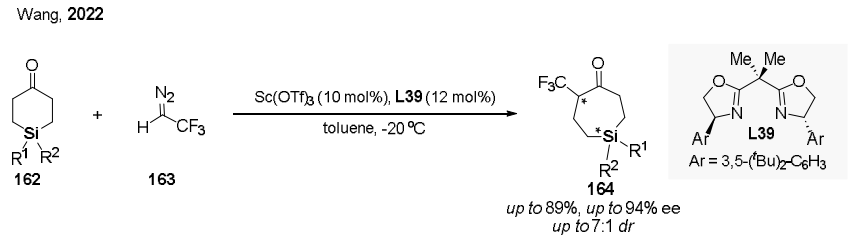
In 2018, an asymmetric Rh-catalyzed cascade reaction was developed by the Tanaka group to synthesize benzofuranylmethylidenebenzoxasiloles (Scheme 30).[67] Desymmetrization of dialkynylsilanes **160** proceeded smoothly *via* 1,2-Si-migration/1,3-C-migration/oxycyclization, furnishing the target products **161** in high yields although with moderate enantioselectivities.



Scheme 30. Synthesis of chiral benzofuranylmethylidenebenzoxasiloles *via* desymmetrization of dialkynylsilanes.

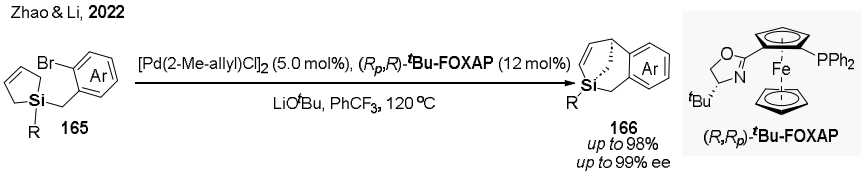
In 2022, the Wang group developed an enantioselective Sc-catalyzed homologation with the chiral bisoxazoline **L39**.[68] 2,2,2-Trifluorodiazoethane **163** reacted with cyclic ketones **162** to afford both carbon- and

silicon-stereogenic α-trifluoromethyl cycloalkanones **164** in up to 94% ee albeit with moderate diastereoselectivities (Scheme 31).



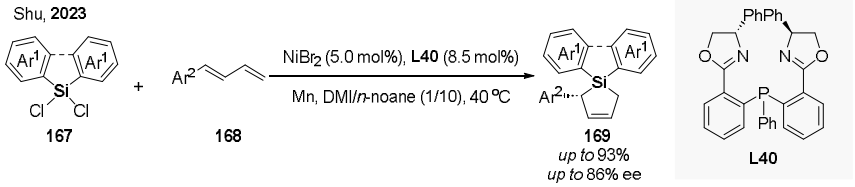
Scheme 31. Synthesis of chiral silacycles *via* Sc-catalyzed homologation.

Meanwhile, Zhao, Li and co-workers realized the construction of sila-bridged bicyclic skeletons featuring both C- and Si-stereocenters (Scheme 32).[69] In this study, *ortho*-bromo benzyl-substituted silacyclopentenes **165** underwent intramolecular Heck-type cyclization to give **166** with high chiral induction using Pd/(R,R_p)-^{t}**Bu-FOXAP**. DFT calculations suggested that the high ee values originated from ligand-controlled kinetic stereo-differentiation during the migratory insertion step.



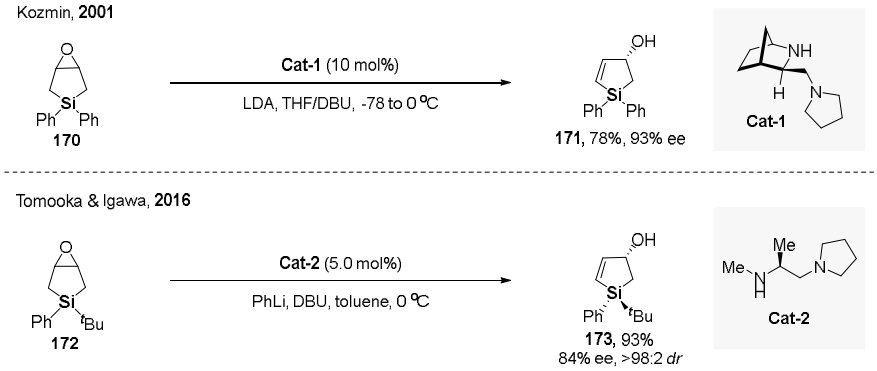
Scheme 32. Synthesis of sila-bridged bicycles *via* intramolecular Heck-type cyclization.

In 2023, a Ni-catalyzed reductive [4+1]-cycloaddition of conjugated dienes **168** with dichlorosilanes **167** has been developed by the Shu group.[70] With this new established protocol, a set of five-membered silacycles were accessible. The enantioselective variant was also realized by using *P,N,N*-tridentate ligand **L40**, giving C-stereogenic **169** in up to 86% ee (Scheme 33). Moreover, spiro silacycles were also obtained when cyclic dichlorosilanes were employed.



Scheme 33. Synthesis of C-stereogenic silacycles *via* reductive [4+1]-cycloaddition.

Besides the utilization of transition metal, main group metals have also been employed as catalysts for preparing the chiral silacycles. In 2001, the Kozmin group reported the desymmetrization of silacyclopentene oxide **170** (Scheme 34, top).[71] By leveraging the chiral bicyclic amine **Cat-1** as a pre-catalyst in the presence of lithium diisopropylamide (LDA), the lithium amide was generated *in situ* as active catalyst species. Cyclic allylic alcohol **171** was obtained in 78% yield and 93% ee *via* enantioselective deprotonation and sequential *β*-elimination. Five years later, the reaction was revisited by Tomooka, Igawa and co-workers, where **Cat-2** was introduced as pre-catalyst (Scheme 34, bottom).[72] The target product **173** bearing both silicon- and carbon-stereogenic centers was given efficiently from **172** with excellent diastereoselectivity and good enantioselectivity.



Scheme 34. Synthesis of chiral silacycles *via* deprotonation and sequential *β*-elimination.

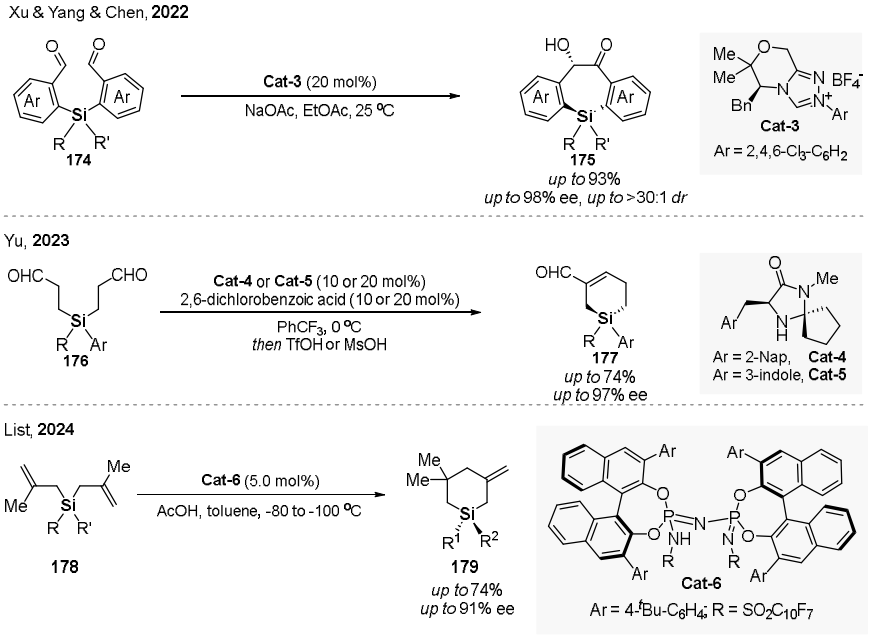
3. Construction of chiral silacycles *via* organocatalysis

Compared with transition-metal catalytic approaches for the access of chiral silacycles, the development *via* organocatalysis has lagged behind. In 2022, Xu, Yang, Chen and co-workers realized an NHC-catalyzed desymmetrization of siladials **174** *via* an intramolecular benzoin reaction (Scheme 35, top).[73] L-phenylalaninol-derived NHC **Cat-3** was employed as pre-catalyst, enabling the access of carbon- and silicon-stereogenic dibenzo[*b*,*f*]silepin-10-ones **175** with good to excellent enantioselectivities and moderate to excellent diastereoselectivities. The next year, the Yu group realized the desymmetrization of siladials **176** for constructing Si-stereogenic cyclic 1,2,5,6-tetrahydrosilines (Scheme 35, middle).[74] In this work, six-membered silacycles **177** were obtained in up to 97% ee *via* an enamine-catalyzed intramolecular aldolization employing a co-catalyst system containing chiral imidazolidinone **Cat-4** or **Cat-5** and 2,6-dichlorobenzoic acid. More recently, the List group reported an enantioselective cyclization of bis(methallyl)silanes **178** for the preparation of Si-stereogenic six-membered silacycles (Scheme 35, bottom).[75] With their imidodiphosphorimidate (IDPi) catalyst (**Cat-6**), a range of cyclization products **179** were furnished with high enantioselectivities (up to 91% ee). Notably, the addition of acetic acid was crucial for the efficiency of the reaction, which liberated the active catalyst species from the covalent adduct.

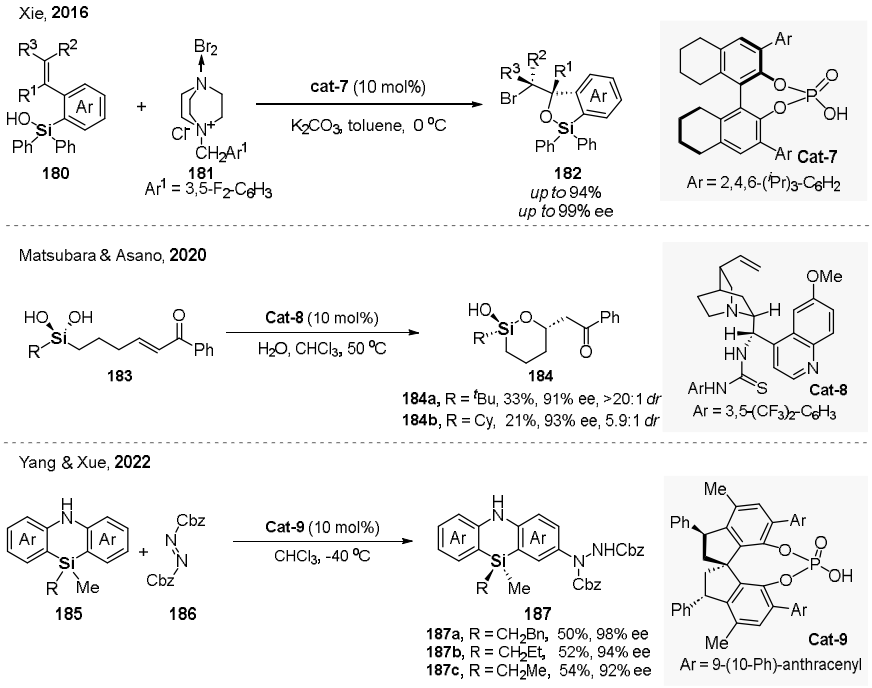
Enantioenriched heteroatom-containing silacycles have also been synthesized *via* organocatalytic approaches. In 2016, the Xie group developed an asymmetric bromo-oxycyclization reaction (Scheme 36, top).[76] Taking advantage of the nucleophilicity of silanol, olefinic silanols **180** reacted with a bromine-*N*-benzyl-DABCO complex **181** as the bromine source in the presence of chiral H_8-BINOL-derived phosphoric acid **Cat-7** catalyst, producing a wide range of chiral benzoxasiloles **182** with moderate to high enantioselectivities. In 2020, an asymmetric cycloetherification has been reported by the Matsubara and Asano group for the access of enantioenriched tetrahydropyrans from *gem*-diols.[77] They also reported the desymmetrization of silanediols **183** in the presence of chiral tertiary amine-thiourea bifunctional catalysis **Cat-8**, which enabled the preparation of oxasilacycles **184** in moderate yields but with high enantio- and diastereoselectivities (Scheme 36, middle). Recently, the Yang and Xue group presented their progress on the construction of the chiral azasilacycles (Scheme 36, bottom).[78] Using **185** and **186** as substrates, Si-stereogenic 5,10-dihydrophenazasilines **187** were obtained with high enantioselectivities *via* asymmetric electrophilic aromatic aminations catalyzed by SPINOL-based phosphoric acid catalyst **Cat-9**.

4. Conclusions

The development in catalytic asymmetric synthesis of chiral silacycles has been comprehensively summarized above. These established methodologies provide straightforward and efficient approaches for diversifying silacyclic compounds, thereby offering novel architectures with potential applications in synthetic chemistry, medicinal chemistry and materials science. Despite these achievements, notable challenges still remain. Current strategies largely limited to the construction of chiral silacycles devoid of heteroatoms.



Scheme 35. Synthesis of Si-stereogenic silacycles by desymmetrization.



Scheme 36. Synthesis of enantioenriched silacycles containing other heteroatoms.

Given the significance of carbon-based heterocycles, developing efficient synthetic methodologies for silicon-based heterocycles including azasilacycles and oxasilacycles with novel structures will be one significant direction in further investigation. Furthermore, existing studies mainly resulted in five- and six-membered cyclic frameworks, while medium- and large-sized chiral silacycles are scarce, thus restricting their broader applications in various fields.

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