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Rhodium-Catalyzed (Asymmetric) Annulation of Silacyclobutanes with Bicyclic Olefins via C−Si Bond Activation

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Cite This: ACS Catal. 2024, 14, 17453−17459 Read Online

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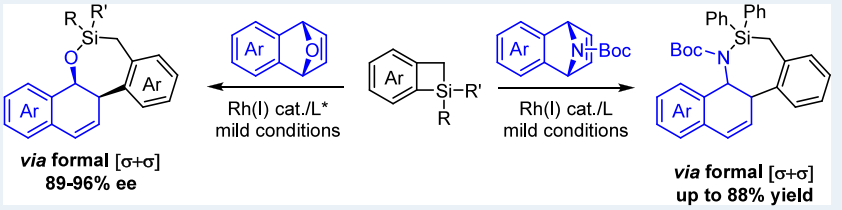


ABSTRACT: The carbon-to-silicon switch gives rise to silacycles that offer eminent biological and photophysical properties. Access to chiral silacycles, especially midsized ones, via intermolecular coupling remains a considerable challenge due to limited synthetic methods. Herein, rhodium(I)-catalyzed annulations between benzosilacyclobutenes (SCBs) and bicyclic olefins are presented. A series of stable seven-membered chiral silacycles have been accessed in high enantioselectivity via the enantioselective [4 + 3] annulation between SCBs and 7-oxabenzonorbornadienes via a formal [2σ + 2σ] C−C and O−Si coupling. The mechanism of the enantioselective [4 + 3] annulation between SCBs and 7-oxabenzonorbornadienes has been investigated, where C−Si oxidative addition of the SCB has been established as the turnover-limiting step.

KEYWORDS: *C−Si activation, bicyclic olefin, rhodium catalysis, silacycle, annulation*

INTRODUCTION

Organosilicon compounds have found wide applications in material sciences and in biorelated studies.[1] The introduction of silicon atoms into carbocycles can greatly affect their properties. This carbon-to-silicon switch can often greatly enhance the lipophilicity while lowering the toxicity of the product. However, strategic and precise introduction of a silicon atom into a chiral cyclic product represents a long-standing challenge, which is related to the high tendency of silicon atoms to form hypervalent species that are prone to decomposition or desilylation. The challenge in synthesis of organosilicon compounds and the versatile reactivity of C−Si bonds as a synthetic handle have aroused increasing attention.[2]

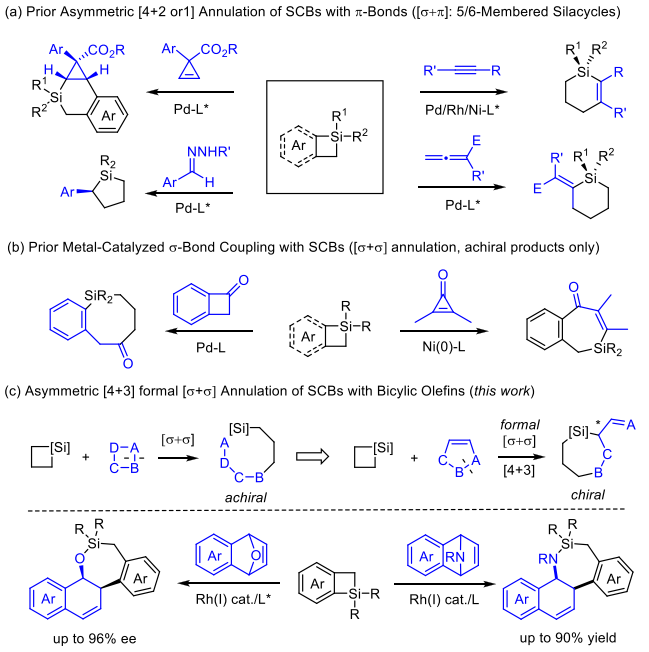
Transition metal catalysis serves as a powerful strategy to access complex organosilicon compounds. Two strategies have been developed by taking advantage of substrate activation toward the synthesis of silicon-containing chiral products. A silicon atom can be selectively installed into aromatic compounds[3] or unsaturated bonds[4] via Si−H cleavage using reactive primary ($RSiH_3$) and secondary (R_2SiH_2) silanes, generating carbon- or silicon-based chirality, as in the seminal studies by Takai et al., He et al., He et al., Meng et al., and others. On the other hand, complex organosilicon products can be obtained via selective C−Si bond cleavage. To lower the barrier of C−Si activation, strain-activated silacycles such as silacyclobutanes (SCBs) have been applied as a powerful silicon source that can undergo a series of transformations.[5] Thus, various unsaturated reagents including olefins,[6] alkynes,[7] and aldehydes[8] have been demonstrated as a π-coupling partner that reacts with SCB in racemic [4 + 2] [2σ + 2σ] reactions. Significantly, Hayashi et al. reported the first intramolecular enantioselective [4 + 2] annulation of SCBs and alkynes.[9] Subsequently, the groups of Zhang et al., Zhao et al., Xu et al., Song et al., Wang et al., and others realized asymmetric [4 + 2][10] and, occasionally, [4 + 1][11] annulation reactions of SCBs with olefins, alkynes, allenes, and carbene reagents (Scheme 1a). Nevertheless, the asymmetric reaction patterns have been predominantly limited to [4 + 2] annulation, and the chiral products are restricted to 5- or 6-membered silacycles with no other heteroatoms.[10,11]

On the other hand, Murakami et al. also demonstrated an alternative class of [2σ + 2σ] reactions between SCBs and a C−C single bond in a strained ring.[12] By following 2-fold ring scission and subsequent formation of C−C and C−Si bonds, challenging midsized silacycles were accessed via [4 + 3] or [4 + 4] annulation (Scheme 1b). Similarly, the C−Si bond in SCB may also undergo inter- or intramolecular coupling with an aryl halide σ-bond via transmetalation.[13] Nevertheless, such

Received: September 16, 2024
Revised: November 2, 2024
Accepted: November 5, 2024

https://doi.org/10.1021/acscatal.4c05675
ACS Catal. 2024, 14, 17453−17459

Scheme 1. Metal-Catalyzed (Asymmetric) Annulation of Silacyclobutanes with Unsaturated Compounds



annulated products have thus far been exclusively restricted to achiral or racemic products. The increasing demand for silacycles in diverse scaffolds calls for the development of efficient and new synthetic methods starting from readily available reagents, especially with excellent chiral induction. We envisioned an alternative strategy of "remote" [2σ + 2σ] annulation between SCBs and an unsaturated coupling partner that affords a seven-membered ring. In this design, the cleavage of a polar single A−B bond embedded in a cyclic olefin results in participation of three atoms in the eventual annulation with an SCB (Scheme 1c), generating a chiral center. 7-Oxa/azabenzonorbornadiene[14] represents such an activated cyclic olefin, and its participation as a three-atom synthon has been reported.[15] We now report C−Si activation of SCBs and [4 + 3] annulation with 7-oxa/azabenzonorbornadienes with 100% atom economy, where excellent enantioselectivity was observed for the coupling of 7-oxabenzonorbornadienes.

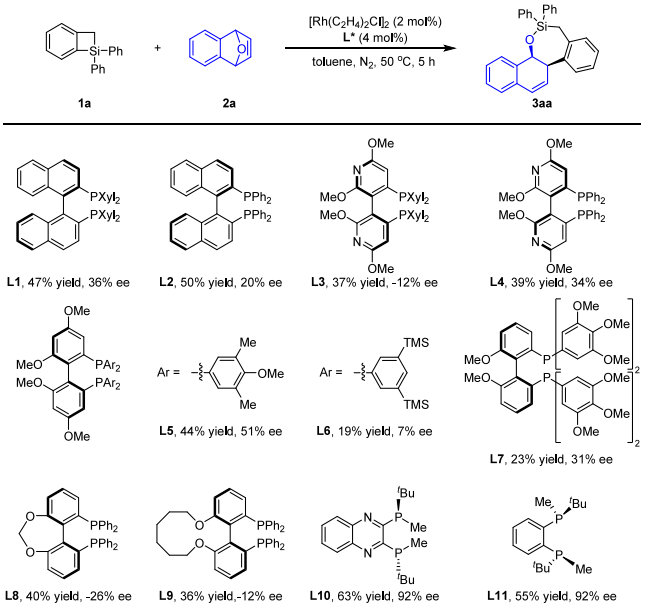
MATERIALS AND METHODS

Materials. All chemicals were obtained from commercial sources and were used as received unless otherwise noted.

Catalytic Reactions. A screw-cap vial (4 mL) was charged with SCB (0.1 mmol, 1.0 equiv), 7-oxabenzonorbornadiene (0.13 mmol, 1.3 equiv), $[Rh(C_2H_4)_2Cl]_2$ (0.8 mg, 2 mol %), and **L10** (1.3 mg, 4 mol %) in dioxane (1 mL), which were stirred in the vial at 60 °C for 5 h under N_2. After cooling to room temperature, the reaction mixture was evaporated under vacuum, and the residue was purified by flash chromatography on silica gel to give the corresponding **3**.

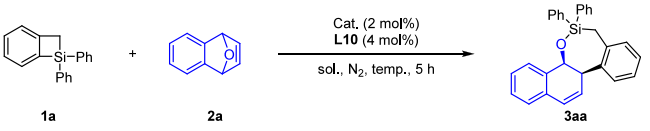
Initial Optimization Studies. We initiated our studies with the screening of the chiral bidentate phosphine ligand for the annulation of an SCB (**1a**) and a 7-oxabenzonorbornadiene (**2a**, Table 1). The rhodium catalyst was selected owing to its powerful cleavage of C−Si and C−C bonds of a series of strained rings.[5] A series of BINAP ligands (**L1** and **L2**) were first employed, and the reaction proceeded with moderate yield and low enantioselectivity to give the desired product (Table 1). The same trend was also found for P-Phos and BIPHEP ligands (**L3**−**L9**). Delightfully, excellent enantioselectivity was observed when QuinoxP* (**L10**) or related BenzP* (**L11**) was

Table 1. Initial Screening of the Chiral Ligands[a]



[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.13 mmol), $[Rh(C_2H_4)_2Cl]_2$ (2 mol %), chiral ligand **L*** (4 mol %) in toluene (1 mL) for 5 h under nitrogen, isolated yield. The ee was determined by high-performance liquid chromatography (HPLC) using a chiral stationary phase.

Table 2. Further Optimization Studies Using L10 as a Ligand[a]

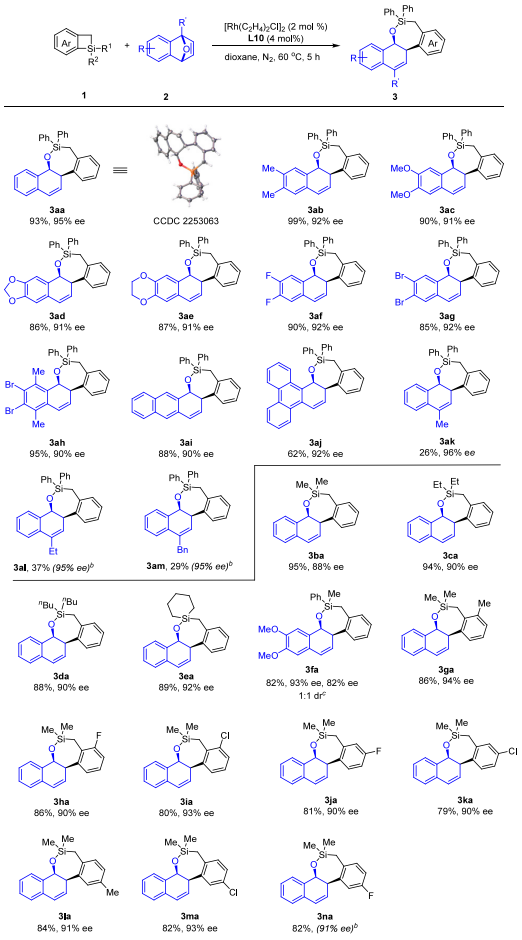


entry	catalyst	temp.	solvent	yield (%)	ee (%)
1	$[Rh(C_2H_4)_2Cl]_2$	50 °C	toluene	63	92
2	$[Rh(C_2H_4)_2Cl]_2$	30 °C	toluene	35	90
3	$[Rh(C_2H_4)_2Cl]_2$	40 °C	toluene	44	91
4	$[Rh(C_2H_4)_2Cl]_2$	60 °C	toluene	85	91
5	$[Rh(C_2H_4)_2Cl]_2$	70 °C	toluene	80	88
6	$[Rh(C_2H_4)_2Cl]_2$	80 °C	toluene	73	89
7	$[Rh(C_2H_4)_2Cl]_2$	60 °C	DCE	57	92
8	$[Rh(C_2H_4)_2Cl]_2$	60 °C	dioxane	93	95
9	$[Rh(C_2H_4)_2Cl]_2$	60 °C	THF	85	90
10	$[Rh(C_2H_4)_2Cl]_2$	60 °C	EtOAc	76	91
11	$[Rh(C_2H_4)_2Cl]_2$	60 °C	PhCl	69	91
12	$[Rh(cod)Cl]_2$	50 °C	toluene	46	83
13	$Pd(dba)_2$	50 °C	toluene	n.d.	
14	$Ni(cod)_2$	50 °C	toluene	n.d.	
15	$Rh(cod)_2NTf_2$	50 °C	toluene	n.d.	
16	$Rh(cod)_2SbF_6$	50 °C	toluene	n.d.	

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.13 mmol), metal catalyst (2 mol %), chiral ligand **L10** (4 mol %) in a solvent (1 mL) for 5 h under nitrogen, isolated yield. The ee was determined by HPLC using a chiral stationary phase. DCE, dichloroethane; THF, tetrahydrofuran; EtOAc, ethyl acetate; PhCl, chlorobenzene; n.d., not detected.

https://doi.org/10.1021/acscatal.4c05675
ACS Catal. 2024, 14, 17453−17459

Scheme 2. Scope of the Asymmetric Annulation of 7-Oxabenzonorbornadiene[a]



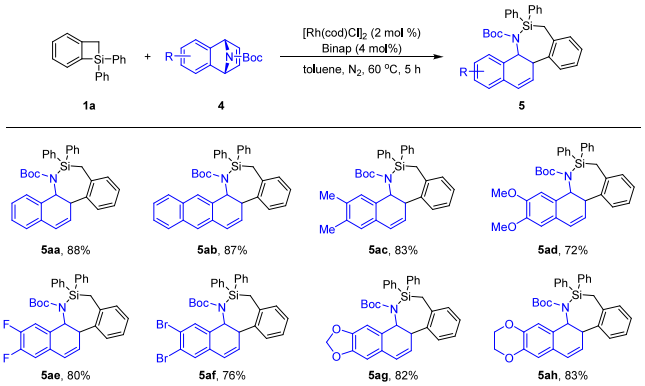
[a]Reaction conditions: **1** (0.10 mmol), **2** (0.13 mmol), [Rh-$(C_2H_4)_2Cl]_2$ (2 mol %), and **L10** (4 mol %) in dioxane (1 mL), 60 °C, 5 h, isolated yield. The ee was determined by HPLC using a chiral stationary phase. [b]The chiral product could not be well resolved into two enantiomers by HPLC using a large number of analytical chiral columns. Instead, the ee was obtained by analysis of the derivatized product upon treatment of the silacyclic product with TBAF (2.0 equiv) in THF. For details, see the Supporting Information for the desilylated product. [c]The dr was determined by ^{1}H nuclear magnetic resonance (NMR) analysis.

used. The former gave slightly higher reactivity, so it was retained for further optimization studies.

Further screening revealed that the temperature had minimal influence on the enantioselectivity in the range of 30−80 °C in toluene (Table 2), although the efficiency was noticeably affected (entries 1−6). Examination of the solvent returned 1,4-dioxane as the optimal one at 60 °C (entries 7−11), under which conditions product **3aa** was obtained in excellent enantioselectivity and efficiency (entry 8). In contrast, poor or no reaction was observed when other neutral or cationic rhodium or other metal catalysts were used (entries 12−16).

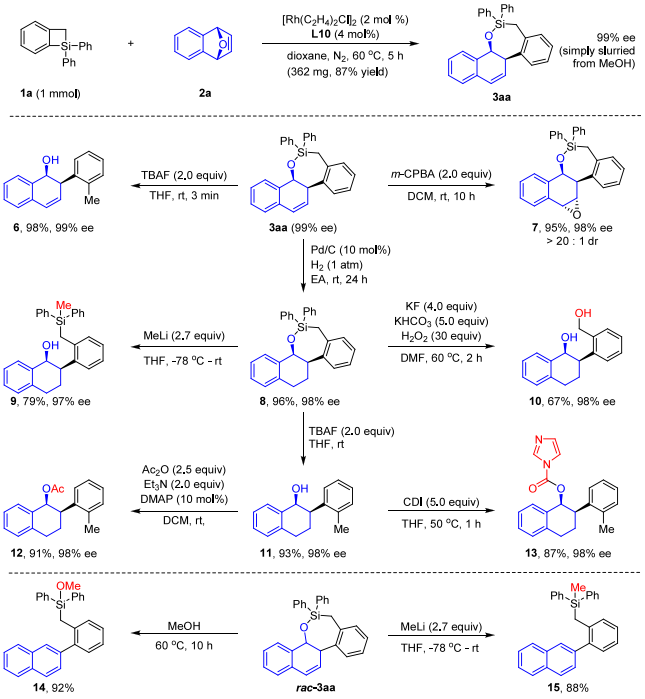
Reaction Scope. With the establishment of the optimal reaction conditions, we next explored the generality of this coupling system. The scope of the 7-oxabenzonorbornadiene substrate was next examined (Scheme 2). Simple and symmetrically substituted 7-oxabenzonorbornadiene in the benzene ring all reacted smoothly under the standard reaction conditions, affording the silacyclic products **3aa**−**3ah** in

Scheme 3. Coupling of Azabenzonorbornadienes in the Synthesis of Racemic Silacycles[a]



[a]Reaction conditions: **1a** (0.10 mmol), **4** (0.13 mmol), $[Rh(cod)Cl]_2$ (2 mol %), (*rac*)-BINAP (4 mol %) in toluene (1 mL), 60 °C, 5 h, isolated yield.

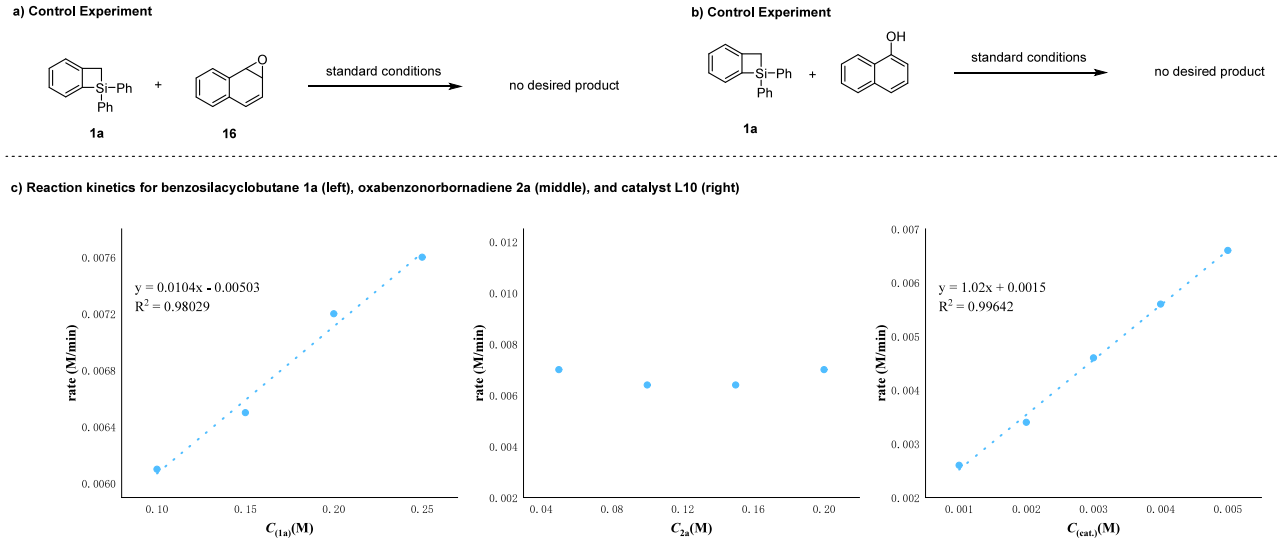
Scheme 4. Synthetic Transformations of Seven-Membered Cyclic Silyl Ethers



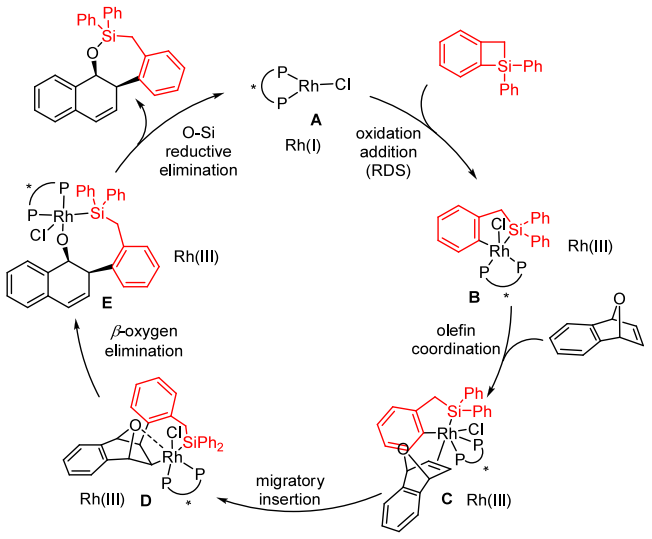
consistently excellent efficiency and enantioselectivity (90−95% ee). The absolute configuration of product **3aa** has been determined by X-ray crystallography (CCDC 2253063). The 7-oxabenzonorbornadiene was also smoothly extended to linearly or T-shaped symmetrically fused ones with no loss of enantioselectivity (**3ai** and **3aj**). The racemic 7-oxabenzonorbornadiene has also been extended to bridge head-monosubstituted unsymmetrical compounds, and the reaction proceeded via kinetic resolution of the olefin. Unlike the high reactivity and clean reactions of symmetrical 7-oxabenzonorbornadienes, decomposition of such 7-oxabenzonorbornadienes was observed. Nevertheless, the desired product was isolated in excellent enantioselectivity and high regioselectivity, albeit in low yield (**3ak**−**3am**, 95−96% ee). In contrast, no desired product was detected when a bridge-head dimethyl-

https://doi.org/10.1021/acscatal.4c05675
ACS Catal. 2024, 14, 17453−17459

Scheme 5. Experimental Mechanistic Studies



Scheme 6. Proposed Catalytic Cycle



substituted symmetrical 7-oxabenzonorbornadiene was employed.

The scope of the SCB substrate was next investigated (Scheme 2). The symmetrical *gem*-disubstituent on the silicon atom was extended to different alkyl groups. Smooth coupling was realized, and the enantioselectivity varied only within a small range (**3ba**−**3ea**, 88−90% ee). An unsymmetrical SCB with phenyl and methyl groups on the silicon center also coupled in high enantioselectivity to give two diastereomers (**3fa**, 93 and 82% ee). However, poor diastereoselectivity (1:1 dr) was observed, suggesting that the carbon chiral center has no chiral induction on the Si chirality during the O−Si formation. Introduction of an alkyl or halo substituent into different positions of the benzene ring of the SCB was also tolerated, and all the products were isolated in excellent enantioselectivity and yield (**3ga**−**3na**). In contrast, no reactivity was observed when an unfused SCB was employed, indicating that the cleavage of the Si−C(aryl) bond to give a Rh−C(aryl) species is crucial for the reactivity.

We next explored the applicability of 7-azabenzonorbornadienes as an analogous coupling partner (Scheme 3). It was found that the racemic coupling of *N*-Boc-protected 7-azabenzonorbornadiene proceeded smoothly with SCB **1a** to afford the cyclic silazane in high efficiency under very similar reaction conditions. A brief survey of the scope of the 7-azabenzonorbornadiene indicated the tolerance of alkyl, methoxy, and halogen groups in the benzene ring. However, the 7-azabenzonorbornadiene has been limited to *N*-Boc-protected ones. In addition, essentially no enantioselectivity has been realized for this reaction after extensive attempts using various classes of chiral phosphine ligands under various conditions.

Synthetic Applications. The synthetic utility of representative seven-membered chiral cyclic silyl ethers was demonstrated (Scheme 4). A scale-up reaction of the coupling of **1a** and **2a** has been conducted at a mmol scale, affording product **3aa** with no loss of efficiency and enantioselectivity. Simple washing of the product with MeOH increased the enantiopurity to 99% enantiomeric excess (ee) in an 87% yield. Upon treatment with tetra-*n*-butylammonium fluoride (TBAF), desilylation of **3aa** afforded chiral secondary alcohol **6** in nearly quantitative yield. Epoxidation of **3aa** occurred selectively to give product **7** as a single diastereomer, and the absolute configuration has been determined by X-ray crystallography (CCDC 2392505; for details, see the Supporting Information). Hydrogenation of the olefin unit then gave tetrahydronaphthalene **8** in excellent yield. Product **8** serves as a useful reagent in diverse transformations. Nucleophilic addition by MeLi provided silyl-tether alcohol **9**. The Tamao−Fleming oxidation of **8** yielded 1,5-diol **10** in good yield. In addition, desilylation of **8** gave benzocyclohexanol **11** whose hydroxy group could be readily protected by an acylating reagent (**12** and **13**). In all cases, essentially no erosion of enantiopurity was observed. On the other hand, the dihydronaphthalene functionality in product **3aa** is prone to aromatization. Treatment of **3aa** with nucleophiles such as MeOH or MeLi led to silyl-retentive aromatization (products **14** and **15**).

Mechanistic Studies. A series of experiments have been conducted to explore the mechanism of the coupling of SCB and 7-oxabenzonorbornadiene (Scheme 5). Linear correlation between the ee of the chiral ligand and that of the product indicated the 1:1 ratio of Rh to **L10** during the

https://doi.org/10.1021/acscatal.4c05675
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enantiodetermining step (see the Supporting Information). To probe the possible intermediacy of an epoxide that might be obtained from isomerization of the 7-oxabenzonorbornadiene, a control experiment has been conducted using epoxide **16** (Scheme 5a). No coupled product was detected under the standard conditions, indicating that the C−O cleavage of the epoxide species is not relevant. In another control experiment using 1-naphthol as a probe, no desired cross-coupling was observed (Scheme 5b). These outcomes verified that the oxabenzonorbornadiene substrate participated directly without the involvement of these two isomerized species. In addition, kinetic studies have been conducted for the substrates and the catalyst (Scheme 5c). The 7-oxabenzonorbornadiene was found to have zeroth-order dependence (Scheme 5c, middle). In contrast, first-order dependence was observed for both the SCB substrate and rhodium catalyst (Scheme 5c, left and right). These data likely suggest that the cleavage of the C−Si bond (oxidative addition) is involved in the turnover-limiting step, while subsequent steps that involve 7-oxabenzonorbornadiene are more rapid (*vide infra*).

On the basis of our experimental studies and prior literature reports,[10,14,15] a plausible catalytic cycle is proposed (Scheme 6). Chelation of phosphine **L10** gives active Rh(I) species **A**. Subsequent rate-limiting Si−C(aryl) oxidative addition occurs to give rhodacyclic intermediate **B**. Following the coordination of the olefin unit in oxabenzonorbornadiene **2a**, the Rh-aryl bond in resulting intermediate **C** undergoes selective migratory insertion to give Rh(III) alkyl intermediate **D** possibly with bridge-head oxygen assistance. Then, β-oxygen elimination releases the ring strain to give an eight-membered Rh(III) alkoxide species **E**, which is proposed to undergo O−Si reductive elimination to furnish the final [4 + 3] product. The migratory insertion is likely enantio-determining because, compared to the insertion, the subsequent β-oxygen elimination is driven by the ring strain and it may bear a lower barrier. In the case of an azabenzonorbornadiene, the migratory insertion occurred with the nitrogen distal to the rhodium center and with the assistance of Boc-carbonyl, which generates a loose chiral pocket, which results in essentially no enantioselectivity.

CONCLUSIONS

In summary, we have realized rhodium(I)-catalyzed annulations between benzosilacyclobutenes (SCBs) and bicyclic olefins. In the case of 7-oxabenzonorbornadienes, the enantioselective [4 + 3] annulation between SCBs afforded a series of stable seven-membered chiral silacycles in excellent enantioselectivity via C−C and O−Si coupling. Both symmetrical and nonsymmetrical 7-oxabenzonorbornadienes are applied, and [4 + 3] coupling occurred via desymmetrization and kinetic resolution, respectively. 7-Azabenzonorbornadienes were also applicable in the corresponding racemic reaction with SCB. The mechanism of the enantioselective [4 + 3] annulation between SCBs and 7-oxabenzonorbornadienes has been explored by kinetic studies and control experiments, where C−Si oxidative addition of the SCB has been established as the turnover-limiting step. The unusual reaction pattern and the unique chiral platform of the products may inspire further studies on activation of the C−Si bond in asymmetric synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c05675.

Detailed experimental procedures, characterization data, and NMR spectra of new compounds (PDF)

Accession Codes

Deposition numbers 2253063 (for **3aa**) and 2392505 (for **7**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service (www.ccdc.cam.ac.uk/structures).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (nos. 22301171 and 22371175) and by the SNNU. Financial support from the fundamental research funds for the central universities (GK202306003) is gratefully acknowledged.

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