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Article

Streamlined Construction of Silicon-Stereogenic Silanes by Tandem Enantioselective C−H Silylation/Alkene Hydrosilylation

Delong Mu,[#] Wei Yuan,[#] Shuyou Chen, Na Wang, Bo Yang, Lijun You, Bing Zu, Peiyuan Yu, and Chuan He*

Cite This: https://dx.doi.org/10.1021/jacs.0c04863
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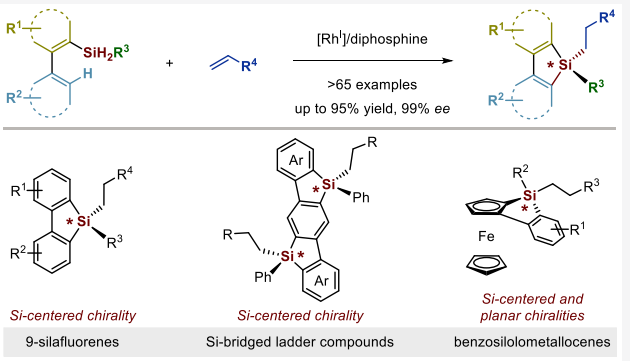
ABSTRACT: A rhodium-catalyzed tandem enantioselective C−H silylation/alkene hydrosilylation of dihydrosilanes, which enables the streamlined construction of a wide range of silicon-stereogenic silanes, is successfully developed. This process involves a SiH_2-steered highly enantioselective C−H silylation to furnish the corresponding desymmetric monohydrosilanes, which are subsequently trapped with alkenes in a stereospecific fashion to build functionally diverse asymmetrically tetrasubstituted silanes. This general strategy combines readily available dihydrosilanes and alkenes to construct various enantioenriched silicon-stereogenic silanes, including 9-silafluorenes, Si-bridged ladder compounds, and benzosilolometallocenes, in a single step with good to excellent yields and enantioselectivities.



INTRODUCTION

The development of new chemical transformations based on asymmetric catalysis for the construction of silicon-stereogenic silanes is of great importance and a challenge.[1] Despite many organosilicon compounds having been prepared by synthetic chemists, which display valuable and desirable properties that have led to their broad applications in synthetic chemistry, materials science, and pharmaceuticals,[2] the creation of silicon-stereogenic centers in enantioenriched forms has been significantly less explored. The inherently longer C−Si bond prevents the formation of compact transition states; and the silicon atom is usually bonded with relatively similar groups, making discrimination of enantiotopic faces or groups difficult.[3] Moreover, the availability of empty 3d orbitals of silicon makes it easy to form hypervalent five- or six-coordinated intermediates.[1d] Traditionally, the preparation of silicon-stereogenic silanes in enantiopure or enantioenriched form is restricted to optical and kinetic resolution with chiral auxiliary,[1a,b,d,4] which severely hamper the discovery and development of this important class of molecules. Therefore, the exploration of efficient and straightforward asymmetric catalysis methods that enable the streamlined construction of enantioenriched highly functionalized silicon-stereogenic silanes from simple starting materials would have far-reaching implications for both the synthetic and the materials chemistry communities. In the past 2 decades, a number of research efforts have been dedicated to the use of chiral transition-metal catalysts that can perform catalytic asymmetric transformation of tailored silanes to enantioenriched silicon-stereogenic silanes via selective desymmetrization of dihydrosilanes or tetraorganosilanes (Scheme 1a).[1g,5] These approaches can provide enantioenriched silicon-stereogenic silanes, but not without limitations, such as (1) the relatively poor substrate scope, functional-group tolerance or enantiomeric excess (*ee*); (2) lack of a streamlined method to construct architecturally complex and functionally diverse silicon-stereogenic silanes from simple starting materials with operational simplicity and efficacy.

In recent years, the development of transition-metal-catalyzed silylation of C−H bonds has emerged as a powerful tool for the synthesis of organosilicon compounds.[6] Usually, the reaction is initiated by oxidative addition of the Si−H bond to the metal center in which the metal atom is oriented to the proximal C−H bond site, allowing selective and efficient C−H bond cleavage.[6b,7] As part of an overarching goal to develop new modes for catalytic enantioselective C−H bond functionalization, we questioned whether the silyl group is not only served as a directing group, but also stands as a silicon-stereogenic center during the enantioselective C−H functionalization, which would provide a more efficient and straightforward manner for the construction of silicon-

Received: May 4, 2020

https://dx.doi.org/10.1021/jacs.0c04863
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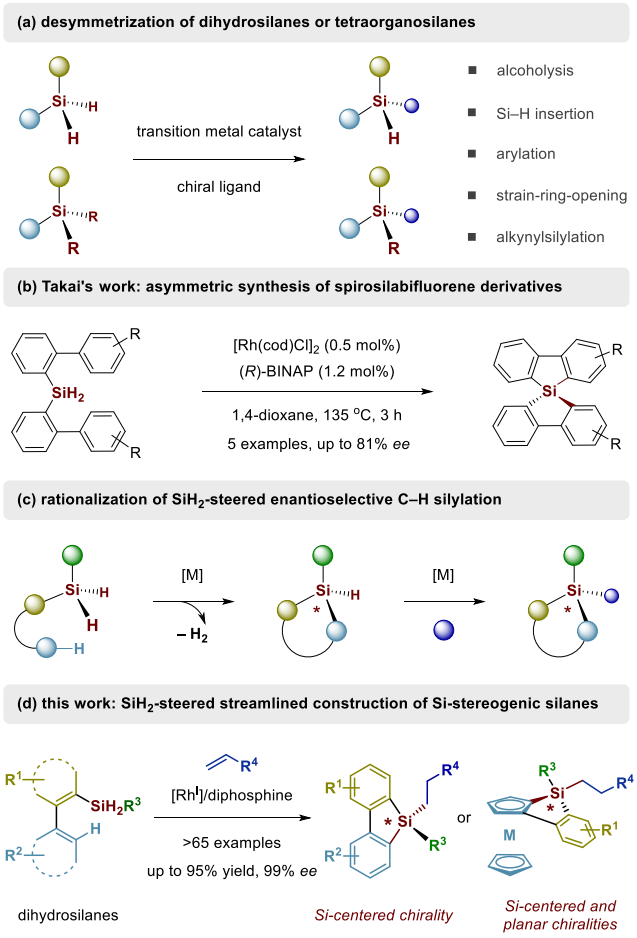
Scheme 1. Construction of Silicon-Stereogenic Silanes

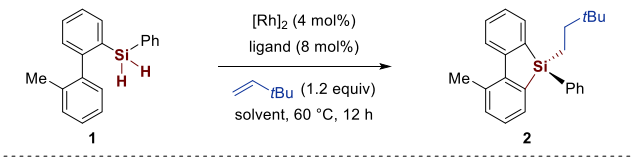


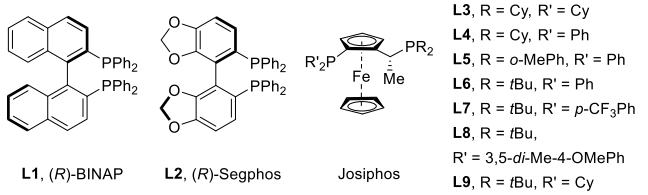
stereogenic silanes with many exciting opportunities. To achieve this idea, a silyl group with two Si–H bonds ($-SiH_2$) is required to conduct the enantioselective C–H bond functionalization via a desymmetrization strategy. However, the main obstacle when using dihydrosilanes is the facile decomposition and nonselective hydrosilylation in the presence of highly active transition metals.[5a] So far, there is only one example involving enantioselective C–H activation of dihydrosilanes reported by Takai, Kuninobu, and co-workers, which enables the synthesis of spirosilabifluorene derivatives from bis(biphenyl)silanes (Scheme 1b).[8] To explore the toolbox of SiH_2-steered enantioselective C–H activation for the streamlined construction of diverse silicon-stereogenic silanes, we propose that reaction of an appropriate chiral transition-metal catalyst with a general dihydrosilane substrate would allow a SiH_2-steered enantioselective C–H silylation affording the corresponding desymmetric monohydrosilane. To avoid the potential decomposition or racemization of the newly formed monohydrosilane, one could use appropriate reaction partners to trap the monohydrosilane instantly and deliver the asymmetrically tetrasubstituted silicon-stereogenic silanes in one pot (Scheme 1c). Nevertheless, the precise control of the sequence of this one-pot process could be rather challenging. Herein, we report the development of an enantioselective C–H silylation/alkene hydrosilylation of various dihydrosilanes, which enables the streamlined construction of a wide range of architecturally complex and functionally diverse asymmetrically tetrasubstituted silicon-stereogenic silanes in a single step with good to excellent yields and enantioselectivities (Scheme 1d).

RESULTS AND DISCUSSION

Reaction Development. We commenced our studies of the enantioselective C–H silylation with dihydrosilane **1** as the substrate, which could presumably undergo SiH_2-steered C–H bond activation via a six-membered metallocycle intermediate in the presence of an appropriate transition-metal catalyst. A number of rhodium(I) and iridium(I) catalyst precursors with various chiral ligands were tested in the reaction. However, only a trace of the desired C–H silylation monohydrosilane product was observed, and the dihydrosilane starting material was decomposed in many cases. To address the decomposition problem of the potentially formed monohydrosilane, we employed several reaction partners in the reaction. After many efforts, we found that when dihydrosilane **1** was treated with 4 mol % Rh(cod)Cl dimer catalyst precursor with bidentate phosphine ligands such as BINAP (**L1**) or Segphos (**L2**) in the presence of 1.2 equiv of 3,3-dimethylbut-1-ene, a tetrasubstituted silicon-stereogenic silane product **2** was obtained in 60–75% *ee*, albeit in low yields (Table 1, entries 1 and 2). It is noteworthy that alkene participates in the reaction as a coupling partner rather than the hydrogen

Table 1. Development of the Enantioselective C–H Silylation for Biaryl Dihydrosilane Substrate[a]





entry	[Rh]	ligand	solvent	yield (%)	*ee* (%)
1	$[Rh(cod)Cl]_2$	**L1**	toluene	10	75
2	$[Rh(cod)Cl]_2$	**L2**	toluene	8	60
3	$[Rh(cod)Cl]_2$	**L3**	toluene	49	91
4	$[Rh(cod)Cl]_2$	**L4**	toluene	13	70
5	$[Rh(cod)Cl]_2$	**L5**	toluene	3	32
6	$[Rh(cod)Cl]_2$	**L6**	toluene	77 (75)	91
7	$[Rh(cod)Cl]_2$	**L7**	toluene	62	82
8	$[Rh(cod)Cl]_2$	**L8**	toluene	68	70
9	$[Rh(cod)Cl]_2$	**L9**	toluene	26	77
10	$[Rh(cod)OH]_2$	**L6**	toluene	44	55
11	$[Rh(nbd)Cl]_2$	**L6**	toluene	18	91
12	$[Rh(CO)_2Cl]_2$	**L6**	toluene	57	70
13	$[Rh(cod)Cl]_2$	**L6**	THF	70	86
14	$[Rh(cod)Cl]_2$	**L6**	DCE	47	87
15	$[Rh(cod)Cl]_2$	**L6**	Et_2O	73	85

[a]Conditions: **1** (0.1 mmol), $[Rh]_2$ (4 mol %), ligand (8 mol %), 3,3-dimethylbut-1-ene (1.2 equiv), in 1.0 mL of solvent under an argon atmosphere at 60 °C for 12 h. The yield was determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard; the yield in brackets is the isolated yield. The *ee* values were determined by chiral HPLC.

https://dx.doi.org/10.1021/jacs.0c04863
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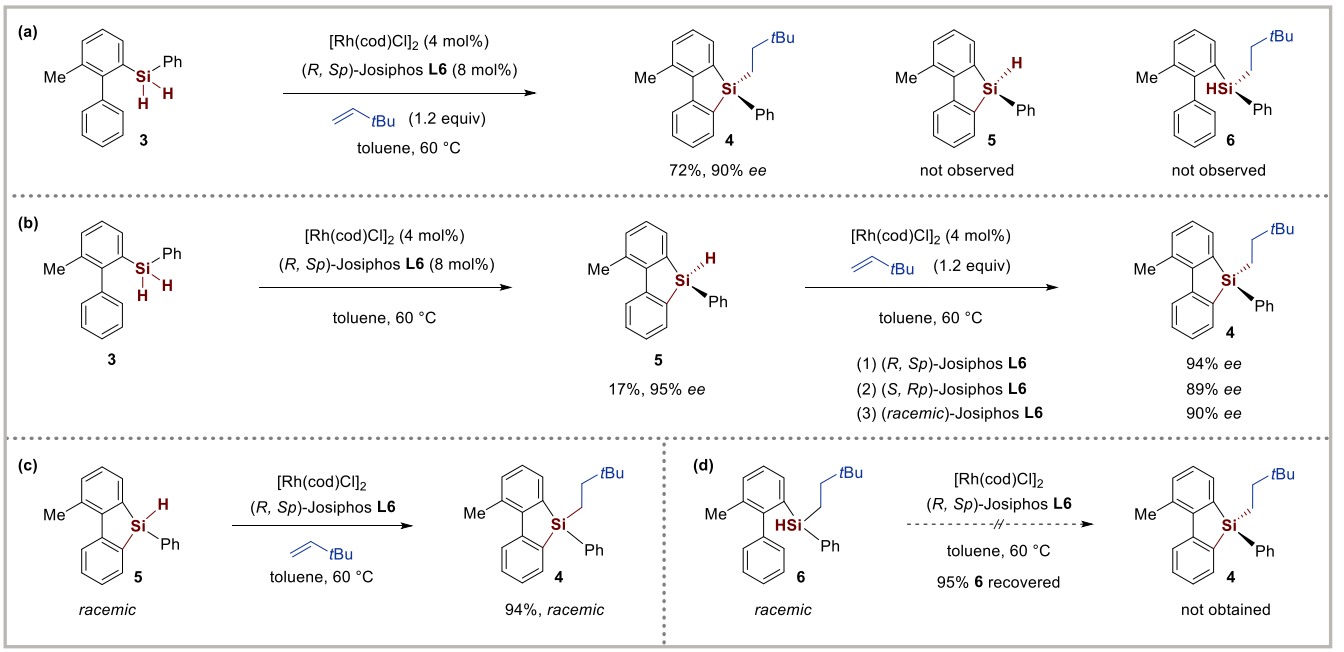
Scheme 2. Control Experiments



Scheme 3. Preliminary Mechanistic Studies

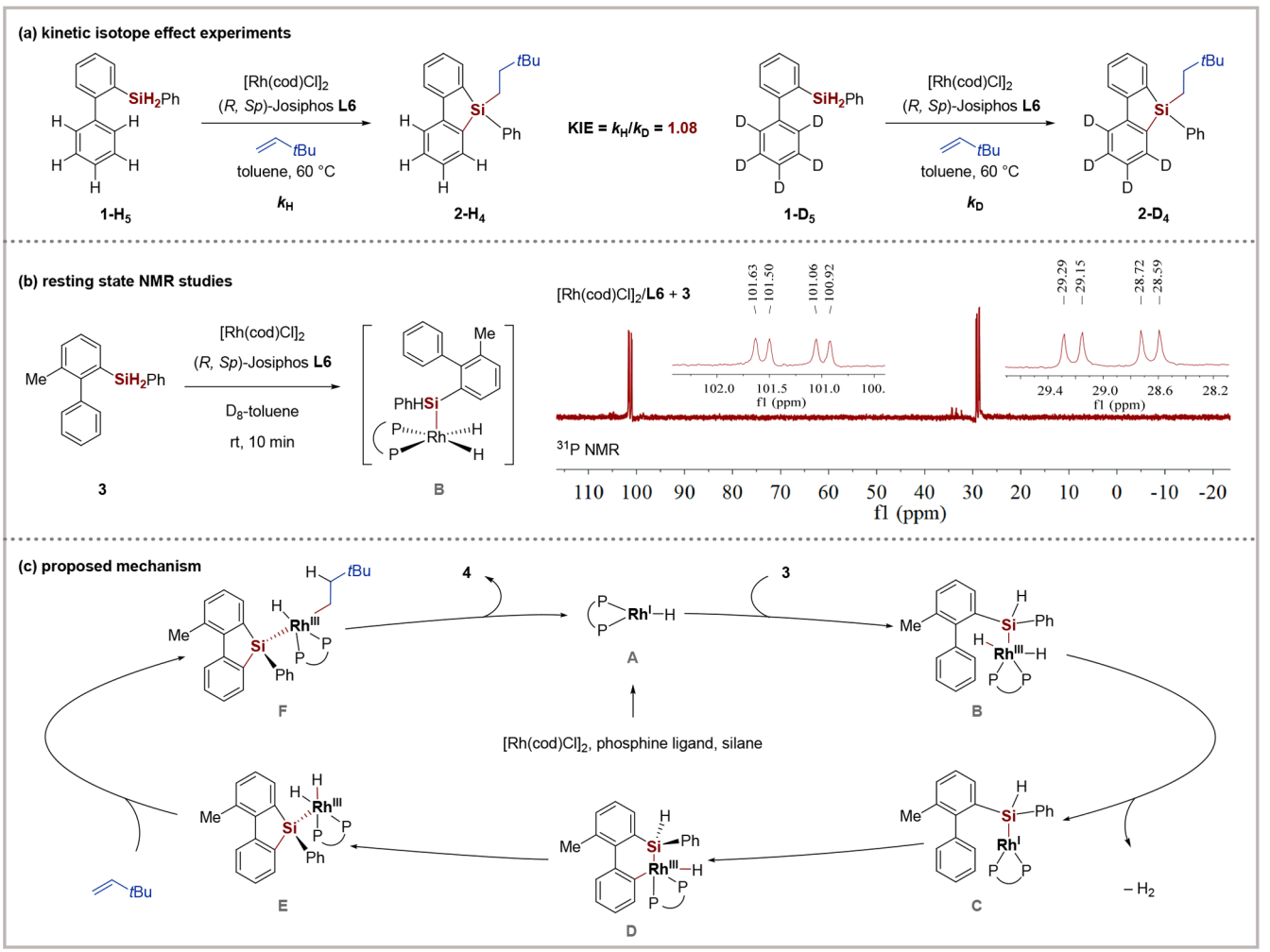


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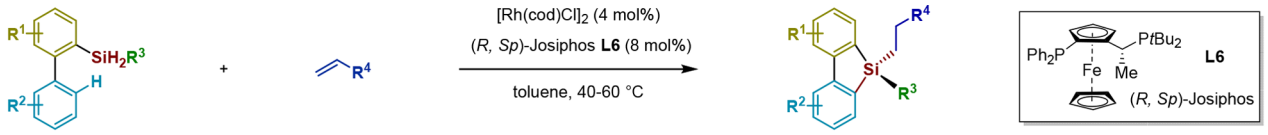
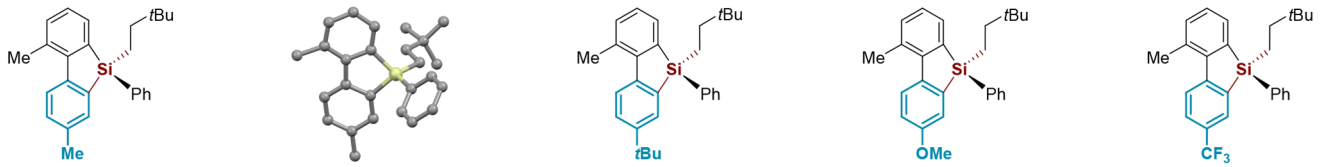
Table 2. Scope of Silicon-Stereogenic Silanes Containing 9-Silafluorene Scaffold[a]





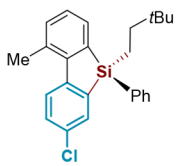
7, 67%, >99% *ee*

7, X-ray structure

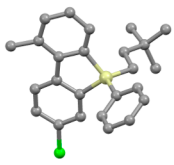
8, 60%, 89% *ee*

9, 75%, 89% *ee*

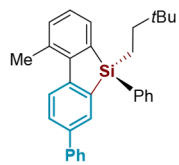
10, 66%, 86% *ee*



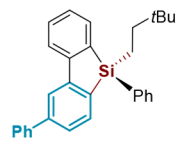
11, 72%, 90% *ee*



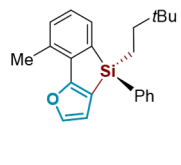
11, X-ray structure



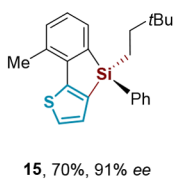
12, 62%, 90% *ee*



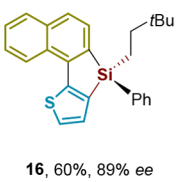
13, 76%, 87% *ee*



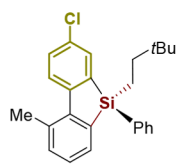
14, 88%, 81% *ee*



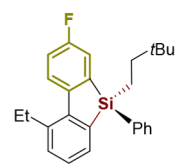
15, 70%, 91% *ee*



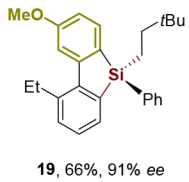
16, 60%, 89% *ee*



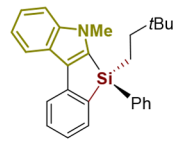
17, 67%, 92% *ee*



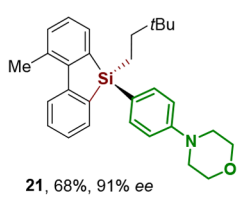
18, 70%, 91% *ee*



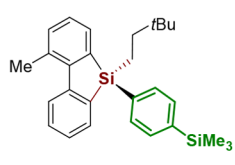
19, 66%, 91% *ee*



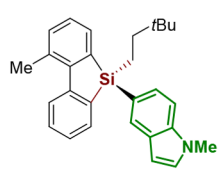
20, 64%, 93% *ee*



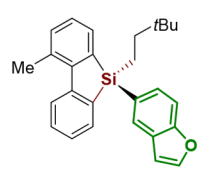
21, 68%, 91% *ee*



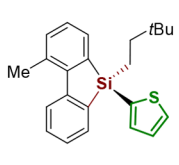
22, 63%, 90% *ee*



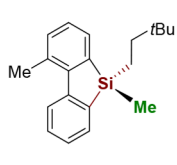
23, 56%, 91% *ee*



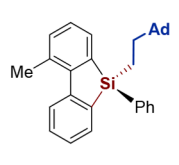
24, 71%, 82% *ee*



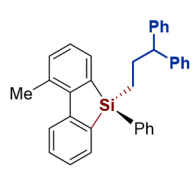
25, 78%, 92% *ee*



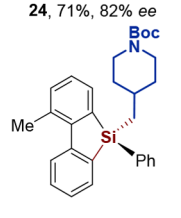
26, 50%, 88% *ee*



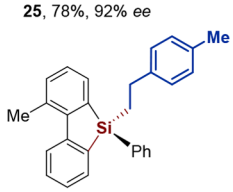
27, 64%, 93% *ee*



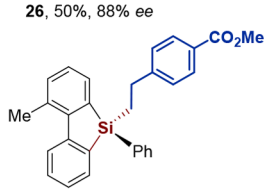
28, 57%, 94% *ee*



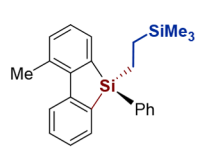
29, 52%, 92% *ee*



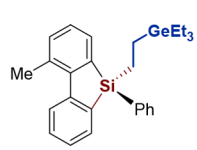
30, 42%, 86% *ee*



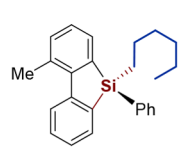
31, 14%, 54% *ee*



32, 85%, >99% *ee*



33, 59%, 88% *ee*



34, 8%, 44% *ee*

[a]See Supporting Information for experimental procedures. Isolated yields. The *ee* values were determined by chiral HPLC.

acceptor, and no extra oxidant is needed in this dehydrogenative silylation process. To the best of our knowledge, this is the first example of a tandem enantioselective silylation of C−H bond/alkene hydrosilylation enabling the construction of a tetraorganosilicon stereocenter from a simple dihydrosilane. Further condition optimization and ligand screening found that one of the commercially available Josiphos ligands (**L6**) improved the yield to 75% with 91% *ee* (Table 1, entries 3−9). Other rhodium(I) catalyst precursors reduced the yields significantly (Table 1, entries 10−12). Changing the solvent to THF, DCE, or Et_2O also gave lower yields and *ee* (Table 1, entries 13−15). Under the optimized conditions, switching to the dihydrosilane substrate **3** containing a methyl-substituted group on the same aromatic ring of the silyl group gave another enantiomer **4** with a comparable 90% *ee* (Scheme 2a). No monohydrosilane **5** or direct hydrosilylation **6** byproduct was observed in this highly selective one-pot process.

https://dx.doi.org/10.1021/jacs.0c04863
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Mechanistic Studies. This interesting transformation displayed a remarkable selectivity that encouraged us to elucidate the reaction mechanism. Usually, hydrosilylation of alkenes with dihydrosilanes is facile under appropriate transition-metal-catalyzed conditions,[5f,m,n,9] and the generated hydrosilylation monohydrosilanes can reasonably undergo the C−H activation/silylation reaction. Therefore, a control experiment in the absence of alkene was reinvestigated. Under the optimized conditions only without the alkene partner, the monohydrosilane product **5** could be obtained in 17% yield via C−H activation/silylation (Scheme 2b). Despite low yield, the comparable 95% *ee* of **5** clearly indicates that the stereodetermining step is the SiH_2-steered C−H activation/silylation process. Further treatment of the resulting enantioenriched monohydrosilane **5** with 3,3-dimethylbut-1-ene under the Rh-catalyzed conditions using either (*R*,*Sp*)-Josiphos **L6** or (*S*,*Rp*)-Josiphos **L6** or (*racemic*)-Josiphos **L6** furnished the identical tetrasubstituted silane product **4** with retention of the absolute configuration (see Supporting Information, section 7.2). When a racemic monohydrosilane **5** was subjected to the reaction conditions using (*R*,*Sp*)-Josiphos **L6**, a racemic product **4** was obtained (Scheme 2c). Moreover, the racemic monohydrosilane **6** was prepared and also subjected to the standard reaction conditions. In this case, no reaction occurred (Scheme 2d). These results further suggest that monohydrosilane **5** is the key intermediate in the reaction, and the chirality of the silicon-stereogenic center of **5** is induced in the first SiH_2-steered C−H activation/silylation process, which leads to the formation of the final product **4**. It should be noted that the key intermediate monohydrosilane **5** is not stable under the Rh-catalyzed conditions, and the one-pot trap of it with alkenes in a stereospecific fashion stabilized the silicon-stereogenic center, providing a perfect strategy for the construction of asymmetrically tetrasubstituted silanes.[5m,10] To the best of our knowledge, this is also the first example of rhodium-catalyzed stereospecific intermolecular hydrosilylation of alkene with retention of the silicon-stereogenic center. In addition, this tandem C−H silylation/alkene insertion process also suggests that the SiH_2-steered intramolecular C−H activation of dihydrosilane is more favored than the intermolecular alkene hydrosilylation.

Next, two parallel kinetic isotope effect (KIE) experiments were carried out using **1-H$_5$** and **1-D$_5$**, as shown in Scheme 3a. The reactions gave rise to a k_H/k_D value of 1.08. The lack of a kinetic isotope effect rules out C−H bond cleavage occurring during the turnover-limiting step in this tandem process.[11] Moreover, the reaction of dihydrosilane **3** with $[Rh(cod)Cl]_2$ and Josiphos **L6** in toluene-d_8 was monitored by ^{31}P and ^{1}H NMR at room temperature (Scheme 3b). Two doublets of doublets at 101.3 ppm (dd, J_{Rh-P} = 140.9 Hz, J_{P-P} = 32.6 Hz, $P(tBu)_2$) and 28.9 ppm (dd, J_{Rh-P} = 136.5 Hz, J_{P-P} = 32.6 Hz, $P(Ph)_2$) were observerd in the ^{31}P NMR spectrum. And two broad rhodium hydride species (−6.28 and −3.32 ppm) were observed in the ^{1}H NMR spectrum (see Supporting Information, section 7.5). These signals suggested the formation of the rhodium silyl dihydride intermediate **B**, which was proposed to be the catalyst resting state in the catalytic cycle.[7a] On the basis of the results described above, we propose that this SiH_2-steered tandem enantioselective C−H silylation/alkene hydrosilylation process occurs by the mechanism as shown in Scheme 3c. First, Rh(I) hydride phosphine active catalyst species **A** is generated from precursor Rh(cod)Cl dimer and chiral phosphine ligand in the presence of hydrosilane,[6b,7] which undergoes oxidative addition into one of the Si−H bonds of dihydrosilane, affording the key intermediate **B**. Then reductive elimination of dihydrogen from intermediate **B** generates a Rh(I) silyl complex **C**, which subsequently undergoes enantioselective C−H bond activation, affording intermediate **D**. Then reductive elimination of intermediate **D** occurs to form the C−Si bond and Rh(I) hydride species, which instantly proceeds oxidative addition into the second Si−H bond, furnishing intermediate **E**. Finally, insertion of alkene into intermediate **E**, followed by reductive elimination from intermediate **F**, completes the catalytic cycle, and it regenerates the catalytically active Rh(I) species. To elucidate the origin of the enantioselectivity, we conducted preliminary DFT calculations (see Supporting Information, section 7.6). We were able to locate the C−H activation transition states **TS-major** and **TS-minor**, which lead to the two enantiomeric products. Various coordination types and conformations were considered to ensure that the most favorable transition states are located. **TS-major** is 5.0 kcal/mol more favorable than **TS-minor** in terms of free energy at room temperature, which is consistent with the observed enantioselectivity. Nonetheless, these DFT results are very preliminary and further detailed studies on the whole reaction pathway is in progress, which will be disclosed in due course.

Substrate Scope. On the basis of the optimized conditions and the preliminary mechanistic studies, we next explored the substrate scope of this process. As the created silicon-stereogenic centers are decorated with four groups, here we used four colors to assess the scope of this reaction (Table 2). First, biaryl dihydrosilane substrates bearing a wide range of substituents on either the reacting C−H bond side of the aromatic ring (light blue) or the silyl group tethered aromatic ring (yellow) at different positions all reacted smoothly with 3,3-dimethylbut-1-ene to afford the desired asymmetrically tetrasubstituted silane products in high yields (55−88%) with good to excellent enantioselectivities (81−99% *ee*). Electron-donating groups, such as methyl, *tert*-butyl, methoxy groups (**7**−**9**, **19**), and electron-withdrawing groups, such as trifluoromethyl group (**10**) and halogen substituents (**11**, **17**, **18**), were well tolerated. Interestingly, compound **11** and compound **17** are also a pair of enantiomers in this transformation. Extended aromatic groups and heterocycles such as furan, thiophene, and indole (**12**−**16**, **20**) could also be transformed into the 9-silafluorene scaffold successfully. Next, changing the third substituents (green) on the dihydrosilane substrates into functionalized aromatic rings, heterocycles, and aliphatic methyl group also produced the corresponding products in good yields without the loss of enantioselectivities (**21**−**26**). For the scope of alkenes (blue), we find that besides 3,3-dimethylbut-1-ene, other types of alkenes containing adamantyl group, aromatic rings, amino group, styrene, vinylsilane, and vinylgermane were competent substrates, providing the desired highly functionalized silane products in good yields with excellent enantioselectivities (**27**−**30**, **32**, **33**). However, because of the unselective hydrosilylation of carbonyl groups, ester or ketone functional groups gave poor results in the transformation (**31**). In addition, linear aliphatic alkenes (**34**) and vinyl ethers are not very compatible with biaryl dihydrosilane substrates in the tandem process. In these cases, direct hydrosilylation of the less hindered alkene is more favored than SiH_2-steered C−H activation/silylation (see Supporting Information, section 6).

https://dx.doi.org/10.1021/jacs.0c04863
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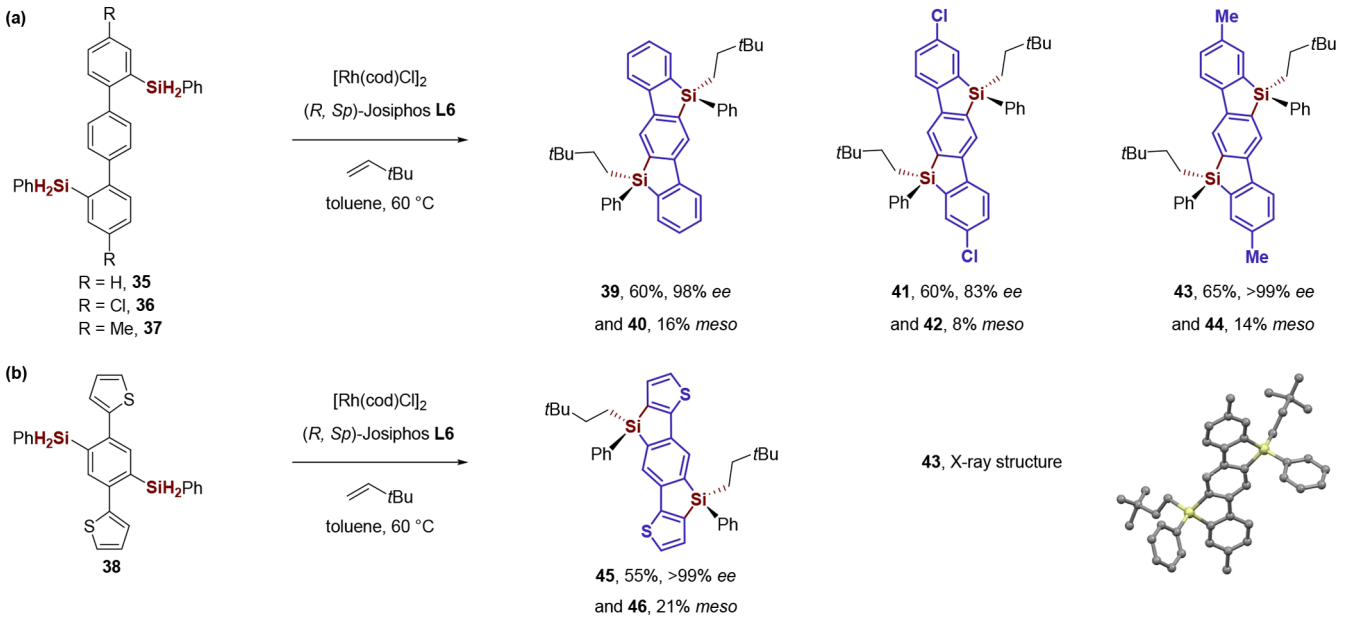
Scheme 4. Construction of Enantiopure Silicon-Bridged Ladder π-Conjugated Systems



It is noteworthy that 9-silafluorene derivatives have attracted increasing attention as promising components of novel advanced functional materials because of their low LUMO energy level via the $\sigma^*-\pi^*$ conjugation.[2i−l] Herein, this methodology provides streamlined access to functionally diverse silicon-stereogenic 9-silafluorene derivatives in a chiral version of untapped potential, which could be highly attractive to organic materials chemists as novel chiral building blocks. Moreover, given that silicon-bridged ladder π-conjugated systems are also an important class of scaffolds for organic electronics,[2i−l] the construction of such molecules in an enantiopure form should be a powerful demonstration of the utility of this process, which would lead to their broad applications in materials science. To test this strategy, we selected four bis-dihydrosilane substrates (**35**−**38**) and subjected them to the reaction conditions (Scheme 4). Each of these bis-dihydrosilanes underwent smooth C−H silylation/alkene hydrosilylation to furnish the target silicon-bridged ladder π-conjugated products (**39**, **41**, **43**, **45**) in good yields with excellent *ee*, albeit minor meso products were also observed.

Since this SiH_2-steered C−H silylation/alkene hydrosilylation enables facile access to silicon-stereogenic 9-silafluorene derivatives in high enantioselectivity, we questioned whether we could expand this process with the metallocene system, producing benzosilolometallocenes containing silicon-stereogenic centers, given that metallocenes are an important class of useful compounds in materials sciences as well as in bioorganometallic chemistry,[12] and chiral metallocene derivatives are also important and privileged units in catalysts and ligands for asymmetric catalysis.[13] On the basis of the established reaction conditions, simply changing the Josiphos ligand into Segphos (**L2**) (for a detailed account of the optimization study, see Supporting Information, Tables S2 and S3), a wide range of ferrocene dihydrosilanes displaying a variety of substituents were found to be suitable substrates for this process (Table 3). The asymmetrically tetrasubstituted benzosilolometallocenes containing both silicon-centered and planar[14] chiralities are obtained as single diastereomers with excellent enantiocontrol (90−99% *ee*). Ferrocene dihydrosilane substrates bearing a number of electron-donating or -withdrawing substituents, such as methyl, fluoro, chloro, methoxy, trifluoromethyl, OTBS, and amino functional groups on the silyl group tethered aromatic rings (yellow and green) at different positions were all well accommodated in this transformation to deliver the corresponding benzosilolometallocene products in 62−95% yields with 93−99% *ee* (**47**−**54**, **58**−**62**). Dihydrosilanes containing a naphthalene ring and benzofuran, as well as ruthenocene (light blue),[14a] were viable substrates giving decent yields and *ee* (**55**, **56**, and **63**). Notably, this process was effective with a broad series of alkenes (blue), including aliphatic alkenes, vinyl ethers, vinyl amines, styrenes, vinyl ferrocene, and vinylsilane (**64**−**74**), which enables the facile construction of complex enantiopure benzosilolometallocenes displaying structural and functional features relevant to fragment-based lead identification programs. It is worth mentioning that linear aliphatic alkene is compatible with the ferrocene dihydrosilane substrate in this tandem process (**66**), which indicates that the SiH_2-steered C−H activation/silylation of metallocene is still more favored than direct alkene hydrosilylation, even with less hindered alkene. To further illustrate the utility of this transformation, we examined this reaction employing the core structures of several bioactive molecules, pharmaceuticals, or materials building blocks, such as (+)-α-tocopherol (**75**), D-ribofuranoside (**76**), β-estradiol (**77**), (−)-menthol (**78**), phenothiaine (**79**), pitavastatin fragment (**80**), and liquid crystal building block (**81**). We were delighted to find that the corresponding benzosilolometallocene products could be obtained in good yields with excellent stereoselectivities, irrespective of existing diverse functional groups and complex molecular structures.

CONCLUSION

Taken together, we develop a tandem highly enantioselective C−H silylation/alkene hydrosilylation methodology, that combines readily available dihydrosilanes and alkenes to construct architecturally complex and functionally diverse enantioenriched tetrasubstituted silicon-stereogenic silanes in a

https://dx.doi.org/10.1021/jacs.0c04863
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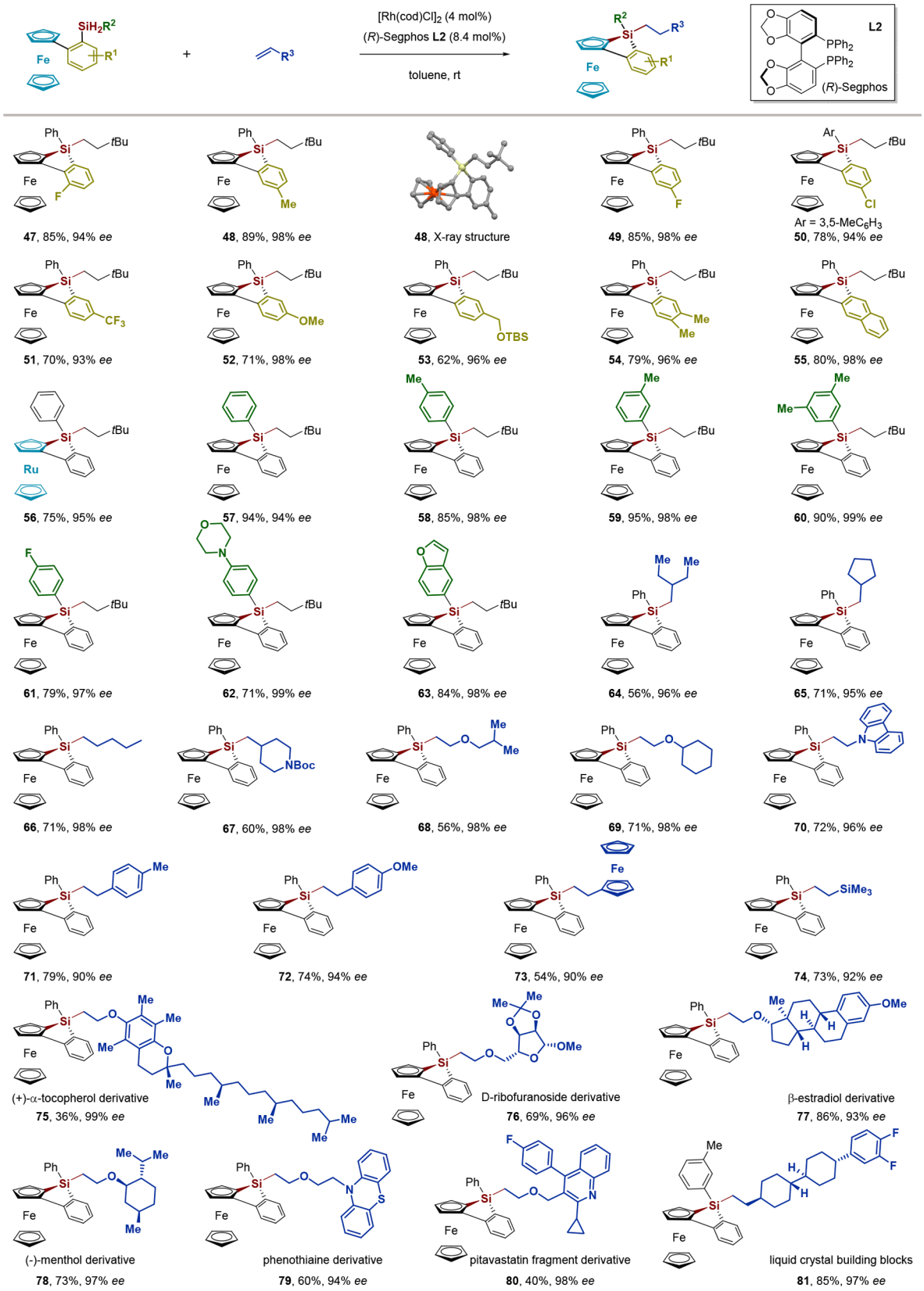
Table 3. Scope of Silicon-Stereogenic Silanes Containing Metallocene Scaffold[a]



[a]See Supporting Information for experimental procedures. Isolated yields. The *ee* values were determined by chiral HPLC. All the benzosilolometallocenes are obtained as single diastereomers (dr > 20:1).

single step with good to excellent yields and enantioselectivities. We expect that the operational simplicity, efficacy, and broad scope of this asymmetrically tetrasubstituted silanes displaying architectural complexity and functional diversity will

https://dx.doi.org/10.1021/jacs.0c04863
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find widespread use in the fields of synthetic chemistry, medicinal chemistry, and also materials science. Moreover, we believe that the convenience of this method generating underexplored SiH_2-directed enantioselective C−H bond activation will inspire further advances in asymmetric catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c04863.

Crystallographic data for compound **7**; crystallographic data for compound **11**; crystallographic data for compound **43**; crystallographic data for compound (*R*,*Rp*-**48**); crystallographic data for compound (*S*,*Sp*-**48**); crystallographic data for compound (*R*,*Rp*-**48-SiH**) (ZIP)

Materials and methods; experimental procedures; optimization studies; characterization data; mechanistic studies; ^{1}H, ^{13}C, and ^{19}F NMR spectral data; HPLC spectra; and mass spectrometry data of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Chuan He − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China*; orcid.org/0000-0002-9983-7526; Email: hec@sustech.edu.cn

Authors

Delong Mu − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China*

Wei Yuan − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China*

Shuyou Chen − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China*

Na Wang − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China*

Bo Yang − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China*

Lijun You − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China*

Bing Zu − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China*

Peiyuan Yu − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China*; orcid.org/0000-0002-4367-6866

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c04863

Author Contributions

#D.M. and W.Y. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (21901104), the Thousand Talents Program for Young Scholars, the start-up fund from Southern University of Science and Technology, the Shenzhen Nobel Prize Scientists Laboratory Project (C17783101), Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002), and China Postdoctoral Science Foundation (2019M651153), and Shenzhen Clean Energy Research Institute (No. CERI-KY-2019-003). We also thank Dr. Xiao-Yong Chang for assistance in solving the X-ray structures.

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