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Enantioselective Hydroxylation of Dihydrosilanes to Si-Chiral Silanols Catalyzed by In Situ Generated Copper(II) Species

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Dedicated to Prof. Chi-Ming Che on the occasion of his 65th birthday.

Abstract: Catalytic enantioselective hydroxylation of prochiral dihydrosilanes with water is expected to be a highly efficient way to access Si-chiral silanols, yet has remained unknown up to date. Herein, we describe a strategy for realizing this reaction: using an alkyl bromide as a single-electron transfer (SET) oxidant for invoking Cu^{II} species and chiral multidentate anionic N,N,P-ligands for effective enantiocontrol. The reaction readily provides a broad range of Si-chiral silanols with high enantioselectivity and excellent functional group compatibility. In addition, we manifest the synthetic potential by establishing two synthetic schemes for transforming the obtained products into Si-chiral compounds with high structural diversity. Our preliminary mechanistic studies support a mechanism involving SET for recruiting chiral Cu^{II} species as the active catalyst and its subsequent σ-metathesis with dihydrosilanes.

Chiral organosilicon compounds featuring Si-stereogenic centers are important for developing synthetic reagents,[1] bioactive molecules,[2] and materials.[3] Among others, Si-chiral compounds with stereogenic Si–O bonds are of particular importance given their great potential for further synthetic transformations.[4] In addition, they are also emerging as promising drug candidates,[5] optically active materials,[6] and chiral ligands[7] (Figure 1A). Thus, efficient catalytic asymmetric methodologies for practical access to these molecules are in high demand, yet have so far remained underdeveloped.[8] In this aspect, the catalytic enantioselective alcoholysis (silanolysis) of prochiral dihydrosilanes[9] with achiral alcohols[10] (silanols[10b,c]) or water is an ideal approach that is among the earliest investigated catalytic methods for access to Si-chiral compounds due to the ready availability of both starting materials (Figure 1B). However, reported successful examples have been focused on the use of precious metal rhodium catalysts for accessing siloxanes[10b,c,11] and silyl ethers.[10b,c,12] As such, the corresponding catalytic enantioselective hydroxylation of dihydrosilanes to Si-chiral silanols,[13] to the best of our knowledge, has hitherto remained unknown.

Notably, 3d transition metal copper is earth-abundant and inexpensive.[14] And Cu^{I}-mediated hydrosilane alkoxylation has been widely invoked for establishing a myriad of useful transformations involving $Cu^{I}H$ species.[15] Among others, Leighton[16] and Oestreich[17] have independently achieved the synthesis of Si-chiral silyl ethers with chiral alcohols by Cu^{I} catalysis. In addition, Oestreich[18] has also pioneered in establishing a series of (dynamic) kinetic resolution reactions of racemic alcohols. However, for the expedient construction of Si-stereogenic centers, the development of Cu^{I}-catalyzed enantioselective alkoxylation (siloxylation) or hydroxylation of hydrosilanes with achiral alcohols (silanols) or water, respectively, though highly demanded, has so far remained unknown (Figure 1C, left). The major reasons for the underdevelopment seem to be twofold. First, the diagonal positioning of the ligand-

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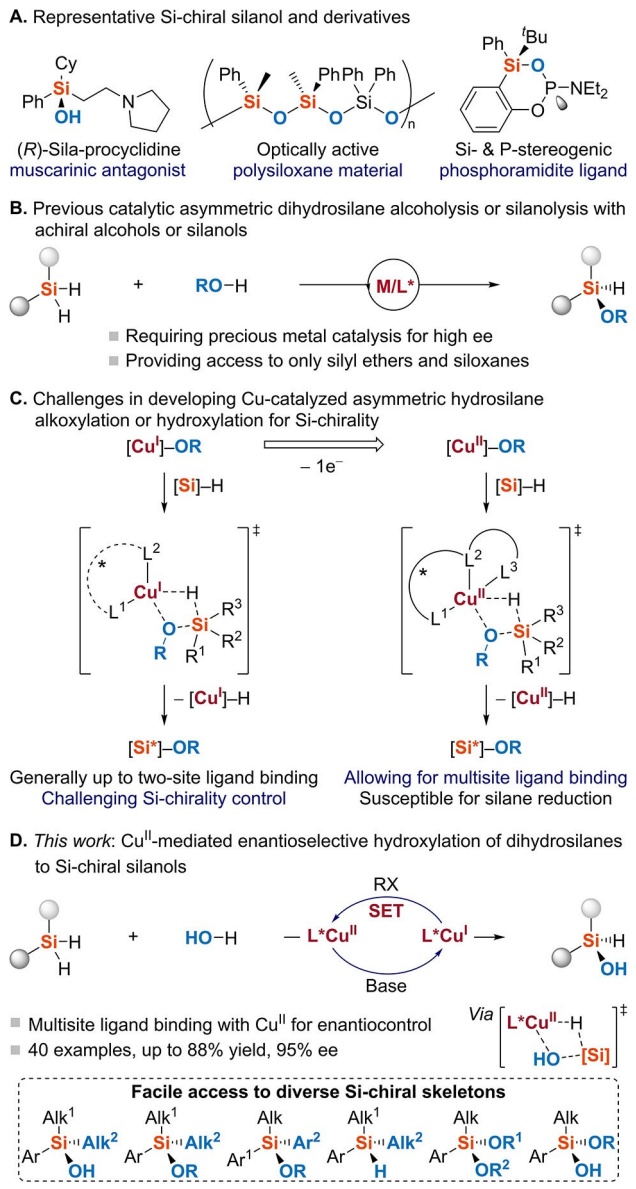

Figure 1. Importance, challenges, and development of copper-catalyzed enantioselective hydroxylation of hydrosilanes to Si-chiral silanols.

coordinated Cu^{I} and the evolving Si stereocenter in the commonly presumed σ-metathesis[19] transition state keeps the chiral ligand far away from the *Si*-substituents. Second, up to two-site ligand binding to Cu^{I} is commonly allowed for the σ-metathesis to proceed,[18–20] which renders the catalyst pocket insufficiently compact. These factors together likely render the enantiocontrol very challenging, particularly when the remarkably sterically small water is employed. In this regard, we noticed that multisite ligand binding to the one-electron oxidized Cu^{II} is possible,[21] which would likely make the catalyst pocket more congested[22] and the stereodifferentiation more effective (Figure 1C, right). Nonetheless, Cu^{II} has been well appreciated to be readily reduced to low-valent species by hydrosilanes.[23] Accordingly, stoichiometric amounts of chiral Cu^{II} complexes seem to be requisite for devising the expected enantioselective alkoxylation (siloxylation) or hydroxylation, which nevertheless is very undesirable in practice.

With our longstanding interest in developing catalytic asymmetric reactions involving radical species,[24,25] we recently disclosed a series of single-electron transfer (SET) catalysts of copper together with chiral multidentate anionic ligands.[26] In these studies, Cu^{I} was continuously oxidized to Cu^{II} through SET[27] with mild oxidants, mostly alkyl halides, as the reactions proceeded. Intrigued by the aforementioned importance of Si-chiral silanols and their synthetic challenges, we envisioned that the use of an SET oxidant together with our copper/multidentate anionic ligand catalysts would be promising for realizing the speculated Cu^{II}-mediated enantioselective hydroxylation of dihydrosilanes. Herein, we report our efforts in achieving this goal using our copper/chiral N,N,P-ligand catalysts under mild conditions (Figure 1D). The introduction of an alkyl bromide to the reaction as the SET oxidant successfully ensures the continuous generation of catalytically active Cu^{II} species. The reaction exhibits high enantioselectivity and good functional group tolerance over a number of structurally distinct dihydrosilane substrates. We further demonstrate the synthetic utility of this methodology by converting the thus obtained Si-chiral silanols into diverse Si-chiral skeletons. Preliminary experimental and computational mechanistic investigations support the SET oxidant role of the alkyl bromide and Cu^{II} species as the active hydroxylation catalyst.

Our investigation began with screening various SET oxidants using dihydrosilane **S1** and water as substrates in the presence of CuI, the Dixon's ligand **L1**,[28] and Cs_2CO_3 in tetrahydrofuran (THF) at 0 °C (Table 1). We previously showed that mildly oxidizing alkyl bromides such as **SX2**–**SX4** were excellent SET oxidants for our Cu^{I}/N,N,P-ligand catalysts.[26b,29] In fact, they all delivered high reaction efficiency and almost constant enantioselectivity (entries 3–5; for results with BnBr, see Scheme S1). By contrast, the stronger peroxide oxidant **SX1** afforded marginal conversion and substantially lower enantioselectivity (entry 2), possibly due to the oxidative decomposition of the copper catalyst. The control experiment without an oxidant indicated the marginal occurrence of essentially non-enantioselective base- and/or Cu^{I}-catalyzed background reactions (entry 1). We next investigated our recently developed N,N,P-ligands **L2**–**L6**,[30] of which all gave remarkably enhanced enantioselectivity (entries 6–10). Particularly, **L6** featuring a benzyl substituent on the oxazoline moiety performed best in terms of both yield and ee (entry 10). We chose **SX4** for these and the following studies due to the relatively low cost, easier product purification, and better performance. The catalyst loading could be decreased to 5 mol % without significantly affecting the overall reaction outcome (entry 11). Further screening of copper salts, base additives, solvents, and temperatures (Table S1) identified the optimal conditions as follows: 0.10 mmol **S1**, 5.0 equiv H_2O, 10 mol % CuI, 10 mol % **L6**, 2.0 equiv Cs_2CO_3, and 2.0 equiv **SX4** in THF (0.1 M) at 0 °C for 1 d, providing **1** in 68 % yield with 95 % ee (entry 10 and Scheme S2A; 70 % yield, 95 % ee on 0.20 mmol scale, Scheme 1). Several Cu^{II} salts gave compa-

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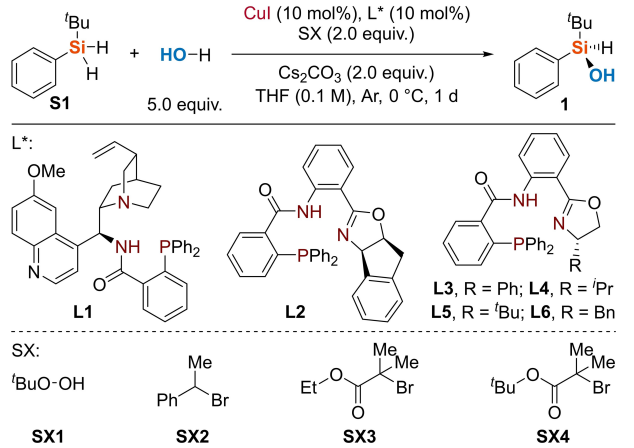
Table 1: Screening of reaction conditions.[a]



Entry	L*	SX	Yield [%]	ee [%]
1	**L1**	none	6	3
2	**L1**	**SX1**	12	10
3	**L1**	**SX2**	66	29
4	**L1**	**SX3**	72	29
5	**L1**	**SX4**	75	29
6	**L2**	**SX4**	16	−69
7	**L3**	**SX4**	11	75
8	**L4**	**SX4**	18	76
9	**L5**	**SX4**	19	75
10	**L6**	**SX4**	68	95
11[b]	**L6**	**SX4**	64	93

[a] Reaction conditions: **S1** (0.10 mmol), H_2O (5.0 equiv), CuI (10 mol%), L* (10 mol%), Cs_2CO_3 (2.0 equiv), and SX (2.0 equiv) in THF (1.0 mL) under argon (Ar) at 0 °C for 1 d. Yield was based on ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The ee values were based on chiral HPLC analysis. [b] CuI (5.0 mol%) and **L6** (5.0 mol%).

rable results with Cu^I (Table S1). Additional control experiments confirmed that all components were indispensable for the reaction (Table S2) and the amount of added water was flexible (Scheme S3).

Regarding the scope of dihydrosilanes (Scheme 1), various additional aryl dihydrosilanes bearing *ortho*-, *meta*- or *para*-substituents of different electronic and steric properties on the phenyl rings were well tolerated (**2**–**18**). Noteworthy is the good tolerance of reactive functional groups such as aryl chloride (**10**), aryl tosylate (**16**), free phenol (**11**), ester (**17**), and carbonate (**18**). This prompted us to further explore other challenging functionalities, such as aryl iodide (**19**), heteroarene (**20** and **21**), amide NH (**22** and **23**), ketone (**24**), alkene (**25**), and nitrile (**26**), of which all proved to be compatible with our reaction conditions. In addition, substrates bearing complex residues derived from bioactive molecules and natural products, such as isoxepac (**27**), phenylalanine (**28**), biotin (**29**), and dehydrocholic acid (**30**), were applicable to our reaction without any functional group or stereochemical interference. Furthermore, aryl dihydrosilanes possessing bicyclic or polycyclic (hetero)aryl rings were also suitable for the reaction (**31**–**36**). The reactions on substrates with the *Si*-aryl ring replaced by trisubstituted alkenyl (**37**) or homobenzyl (**38**) groups or with the *Si*-^{t}Bu substituent switched to α,α-dimethylbenzyl (**39**) or cyclohexyl (**40**) groups still provided promising enantioselectivity albeit with low reaction yield, which are currently under further optimization in our lab. Unfortunately, the phenyl dihydrosilane with a small *Si*-methyl substituent (**41**) and unsymmetric diaryl-substituted dihydrosilanes (**42** and **43**) are currently unsuitable for this reaction due to low yield and poor ee (see Scheme S2B–D for details). The absolute configuration of **36** was established to be *R* on the basis of X-ray structural analysis[31] (Scheme 1 and Figure S1) and those of others were assigned by analogy.

To demonstrate the practicality and synthetic potential of this methodology, we first carried out a gram-scale reaction on **S1** to obtain Si-chiral silanol **1** with comparable efficiency and enantioselectivity (Scheme 2A). We readily obtained the antipode of **1** (*ent*-**1**) with almost the same yield and enantioselectivity using the enantiomer of **L6** (*ent*-**L6**) under the otherwise standard conditions (Scheme 2B). Chiral silanol **1** remained stable, underwent slow condensation reactions, and gradually racemized in neutral, basic, and acidic conditions, respectively. Accordingly, we then devised two strategies for its follow-up transformations (Scheme 2C): (1) direct Si–H carbene insertion followed by silanol manipulation, leading to Si-chiral tertiary silanols **44** and **45**, silyl ether **46**, and hydrosilane **47**; (2) first silanol protection, then Si–H alkoxylation, and finally, chemoselective nucleophilic attack, delivering Si-chiral hydrosiloxane **48**, ethoxysiloxane **49**, all carbon-substituted disiloxanes **50** and **51**, and ethoxysilanol **52**. Of particular note is the rare Si–H ethoxylation reaction, which likely proceeded through a tandem Rh-catalyzed alkene hydrosilylation/concerted Si–O elimination[32] pathway. Most importantly, all the abovementioned transformations did not result in an apparent loss of Si-stereochemical integrity, showcasing the great synthetic power of our methodology.

Concerning the mechanism of this reaction, we initially observed the formation of **53** in the control experiment with radical trapper TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) (Scheme 3A), likely indicating the formation of the corresponding alkyl radical from **SX4** via SET[27] with Cu^I. Besides, the efficiency and enantioselectivity of the control reaction were almost unaffected by this radical trapping process, disproving the possible hydrogen atom abstraction of **S1**[33] by the alkyl radical for product formation. In addition, we observed the formation of a roughly stoichiometric amount of the corresponding radical disproportionation product in the other control reaction using an analog of **SX4** (Scheme S4; see Scheme S5 for details of the radical coupling product from benzylic bromide **SX2**). These results together suggest a dispensable role of this radical in the ensuing Cu^{II}-participated steps. The next control experiment with stoichiometric amounts of Cu^{II} salt and chiral ligand **L6** provided **1** with essentially the same enantioselectivity (Scheme 3B), supporting Cu^{II} species as the active catalyst for the enantioselective hydroxylation. The subsequent control experiments with scalemic ligand **L6** showed a linear relationship between the ee values of ligands and corresponding products (Figure S2), revealing a 1:1 molar ratio of Cu^{II} to the ligand in the enantiodetermining step. In

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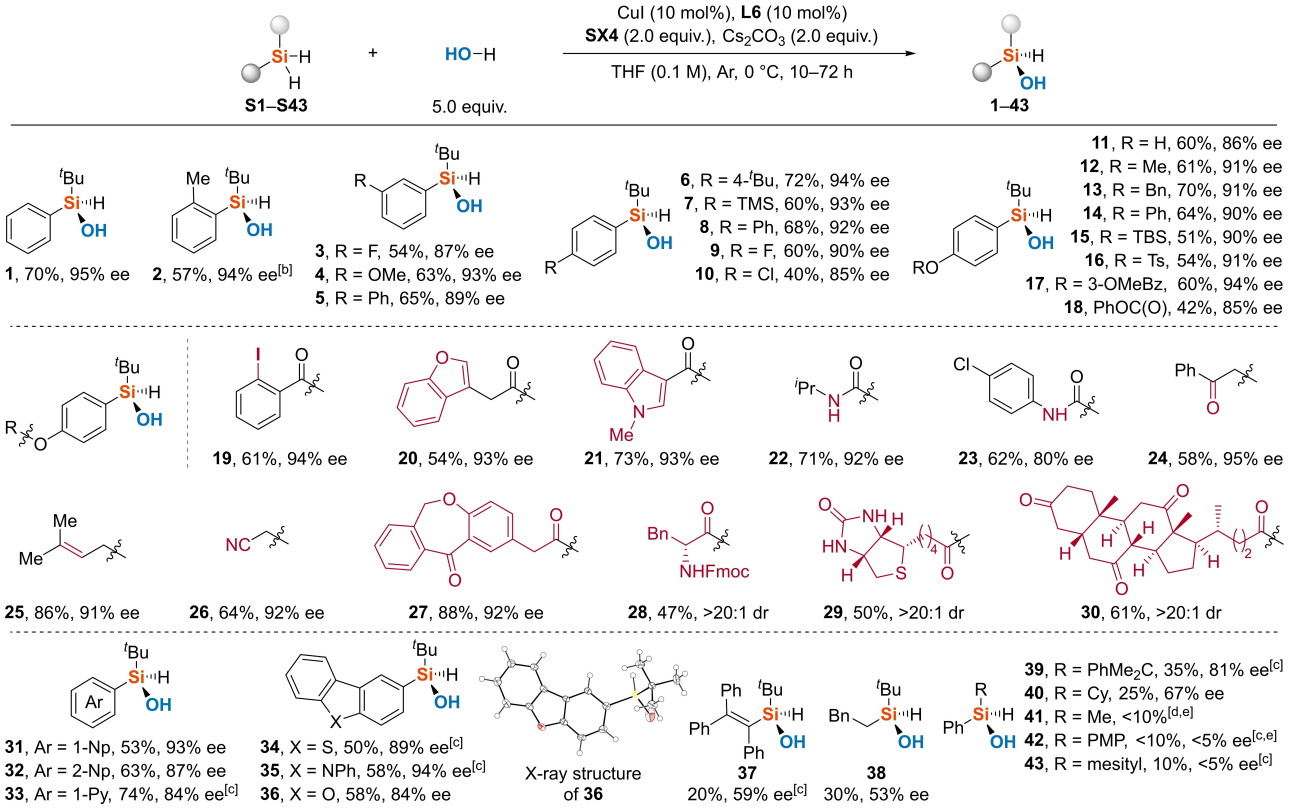

Scheme 1. Scope of dihydrosilanes.[a] [a] Standard conditions: dihydrosilane (0.20 mmol), H_2O (5.0 equiv), CuI (10 mol%), **L6** (10 mol%), Cs_2CO_3 (2.0 equiv), and **SX4** (2.0 equiv) in THF (0.10 M) at 0 °C under argon for 10–72 h. Yield was isolated. The ee values were based on chiral HPLC analysis. [b] CuI (20 mol%) and **L6** (20 mol%). [c] Dihydrosilane (0.10 mmol) was employed. [d] Ee was not determined. [e] Significant formation of disiloxanes and oligosiloxanes was observed. TMS, trimethylsilyl; TBS, *tert*-butyldimethylsilyl; Ts, 4-methylbenzenesulfonyl; Fmoc, 9-fluorenylmethyloxycarbonyl; Np, naphthalenyl; Py, pyrenyl; Cy, cyclohexyl; PMP, *p*-methoxyphenyl.

addition, we also observed a relatively small but significant primary kinetic isotope effect (KIE) using the deuterated **S1** (parallel KIE = 1.8; intermolecular competition KIE = 1.5). Thus, the Si–H bond cleavage is likely involved in the rate-determining steps. Our preliminary density functional theory (DFT) calculations lend further support to the conjectured Cu^{II}-mediated σ-metathesis,[19] which proved to be facile to proceed with an activation barrier of 19.7 kcal mol^{-1} (Scheme 3C and Figure S3; see the Supporting Information for more details and discussions). Interestingly, the efficiency of the stoichiometric control reaction was greatly diminished (Scheme 3B) likely due to competing Cu^{II} reduction by hydrosilanes,[23] which highlights the additional advantage of our reaction design.

On the basis of these results and previous reports, we tentatively proposed a plausible mechanism, as shown in Scheme 3D. First, Cu^{I} salt reacts with ligand L* in the presence of base to generate the L*Cu^{I} complex **I**, entering the catalytic cycle. This complex subsequently undergoes SET[26,27] with alkyl bromide to afford alkyl radical **II** and L*Cu^{II}–Br **III**. The alkyl radical **II** then undergoes off-cycle radical coupling or radical disproportionation and polymerization for termination. Within the catalytic cycle, base-promoted hydrolysis converts **III** to L*Cu^{II}–OH **IV**. Its subsequent σ-metathesis with dihydrosilane **S1** delivers the final enantioenriched silanol product **1** and L*Cu^{II}–H **VI**[23] through a four-membered cyclic transition state **V**.[19] Finally, tandem deprotonation of **VI** by base[34] and comproportionation of the resulting Cu^{0} species with **III**[35] regenerate the complex **I** from **VI**, closing the catalytic cycle. Assuming that the σ-metathesis step was enantiodetermining, we conjectured two transition states *R*-**TS** and *S*-**TS** (Scheme 3E) that led to **1** and *ent*-**1**, respectively. The latter (Scheme 3E, right) was rendered disfavored possibly due to the steric clash between the *Si*-phenyl ring and the hydroxide, leading to the favorable formation of **1**. Further studies are underway in our lab to disclose more details of the reaction mechanism.

In summary, we have developed a practical and robust copper-catalyzed enantioselective synthesis of a wide range of secondary Si-chiral silanols through the hydroxylation of prochiral dihydrosilanes with water. The successful implementation of the reaction hinges on the use of alkyl bromide as an SET oxidant for in situ continuously generating catalytically active Cu^{II} species. In addition, the use of multidentate anionic ligands is also important for ensuring compact σ-metathesis transition states that result in highly efficient enantiocontrol. Further strategic derivatizations of these secondary Si-chiral silanols deliver a variety of Si-chiral skeletons. This work not only provides a practical

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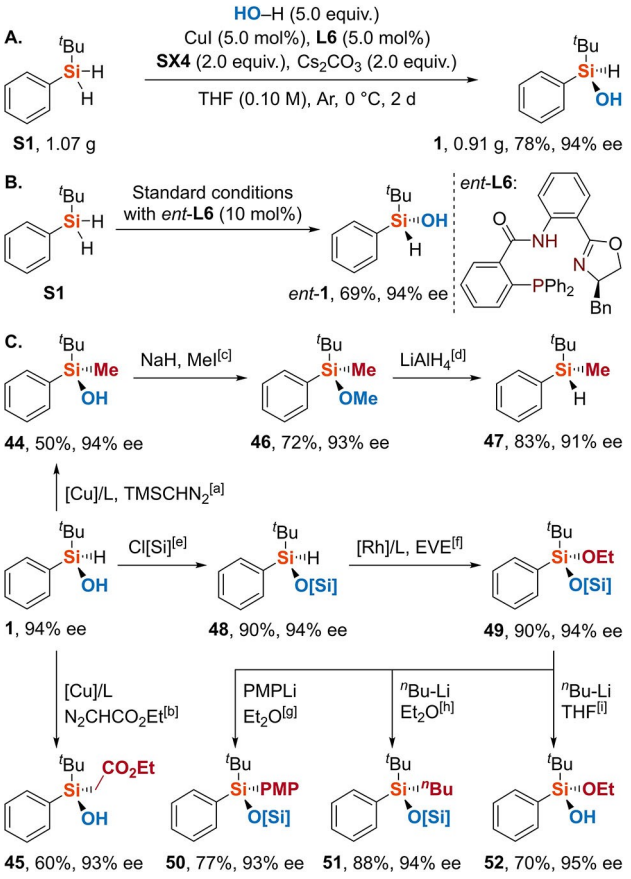
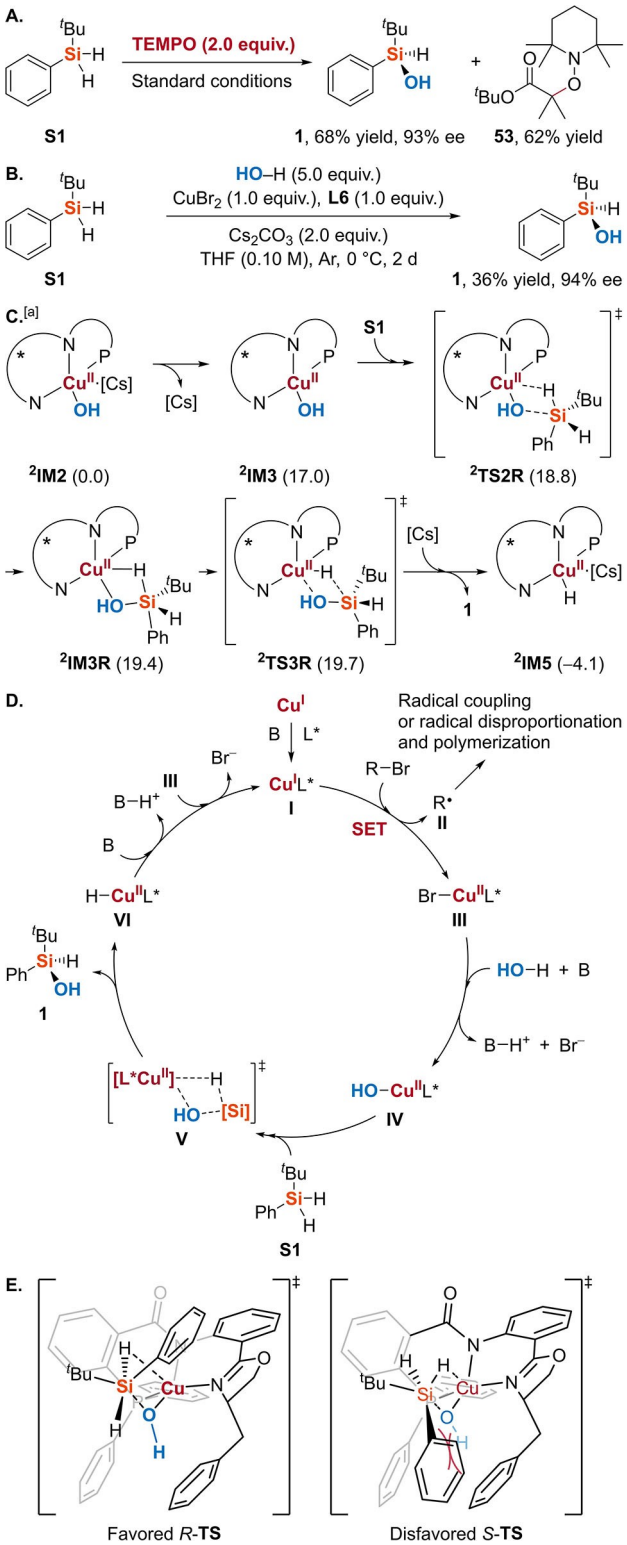


Scheme 2. Scalability and synthetic utility. [a] $Cu(OTf)_2$ (10 mol%), Phen (12 mol%), and $TMSCHN_2$ (2.0 equiv) in CH_2Cl_2 at rt. [b] $Cu(OTf)_2$ (10 mol%), Phen (12 mol%), and N_2CHCO_2Et (2.0 equiv) in CH_2Cl_2 at rt. [c] MeI (10 equiv) and NaH (10 equiv) in THF at rt. [d] $LiAlH_4$ (3.0 equiv) in Et_2O at 40 °C. [e] DMAP (10 mol%), $ClSiPh_2Me$ (1.5 equiv), and imidazole (1.5 equiv) in CH_2Cl_2 at rt. [f] $[Rh(COD)Cl]_2$ (1.0 mol%), *rac*-BINAP (2.0 mol%), and EVE (10 equiv) in PhMe at 60 °C. [g] PMPLi (3.0 equiv) in Et_2O at rt. [h] ^{n}BuLi (3.0 equiv) in Et_2O at rt. [i] ^{n}BuLi (3.0 equiv) in THF at rt. Phen, 1,10-phenanthroline; DMAP, 4-(dimethylamino)pyridine; COD, 1,5-cyclooctadiene; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; [Si], $SiPh_2Me$; EVE, ethyl vinyl ether.



Scheme 3. Mechanistic studies and proposal. [a] The calculation was done with **L6**. [Cs], $CsHCO_3$·CsBr; B, base.

synthetic tool to facilitate the development of Si-chiral organosilicon chemistry but also opens the door for exploring Cu^{II}-mediated enantioselective hydrosilane transformations.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Cambridge Crystallographic Data Centre at https://www.ccdc.cam.ac.uk/structures/, reference number 2143892.

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