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Cu/chiral phosphoric acid-catalyzed radical-initiated asymmetric aminosilylation of alkene with hydrosilane

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The catalytic radical-initiated asymmetric 1,2-aminosilylation of alkene with a hydrosilane under Cu(I)/CPA cooperative catalysis has been developed. This method features the use of hydrosilane as the reductive radical precursor, enabling efficient access to skeletally diverse silicon-containing azaheterocycles including pyrrolidine, indoline and isoindoline bearing an α-tertiary stereocenter with high enantioselectivity. The key to the success includes the use of Cu(I)/CPA cooperative catalyst system and the β-silicon effect of the silyl group to stabilize the *in situ* generated carbocation intermediate.

asymmetric radical chemistry, aminosilylation, alkenes, Cu/chiral phosphoric acid, silyl radical

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1 Introduction

Organosilicon compounds have been gaining significant interest among chemists as powerful synthetic building blocks in the design of organic electronic and photonic materials, polymers, pharmaceuticals as well as agrochemicals because these moieties exhibit improved biological and/or physicochemical properties relative to their parent carbon compounds [1]. Consequently, tremendous efforts have been devoted to the development of practical strategies for preparation of organosilicon compounds with specific structures [1]. Among the established methods, the use of silicon-centered radical as the key intermediate, via hydrogen atom abstraction (HAA) from the inert Si–H bond of the hydrosilane, has been established as a powerful technique in various radical processes over the past three decades [2]. Given the facile accessibility of alkenes, intermolecular addition of radical species to alkenes followed by trapping of another functional group to realize 1,2-difunctionalization of alkenes has emerged as one of the most attractive strategies for the simultaneous formation of two vicinal chemical bonds [3]. In particular, owing to the innate reactivity and unique selectivity of silicon-centered radicals [2], radical-initiated 1,2-silylfunctionalization of alkenes has received increasing attention in recent years [4]. Despite these impressive advances, the development of asymmetric catalytic versions of such transformations, to the best of our knowledge, has so far remained unknown, largely owing to the difficulty related to the stereochemical control of the *in situ* generated alkyl radical species [5].

More recently, Cu(I)-catalyzed radical asymmetric reaction featuring chiral metal species to trap reactive alkyl radical, a strategy pioneered by Fu and others (Scheme 1(a)) [6], has been proven as an attractive strategy for creating

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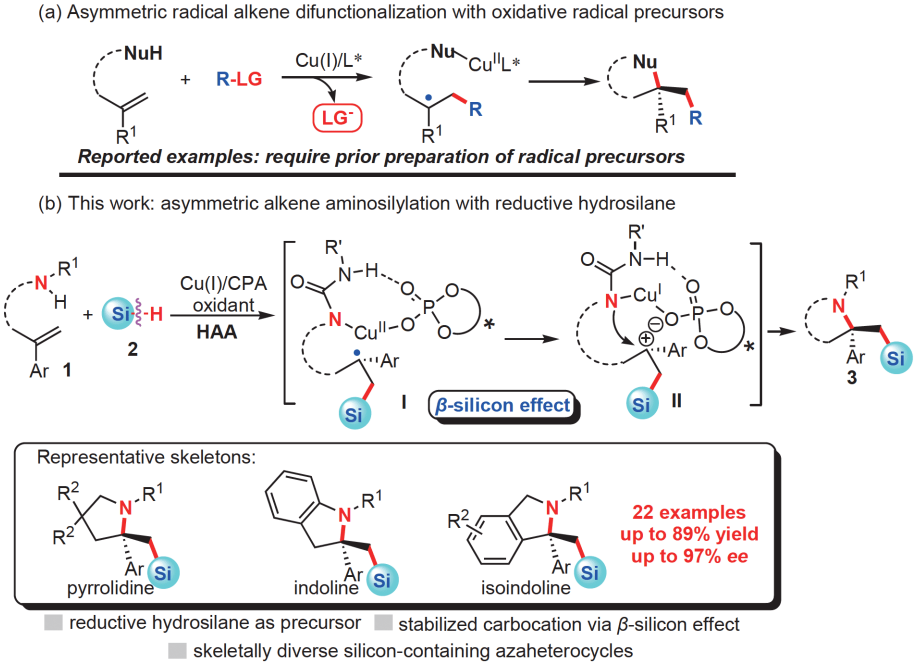
chiral scaffolds. In particular, Buchwald *et al*. and Liu *et al*. [7] pioneered the use of a chiral Cu/bis(oxazoline) system to elegantly realize enantioselective alkene difunctionalizations, respectively. At the same time, our group has developed the copper/chiral anionic ligand system to realize asymmetric transformations [8]. Notably, all of these catalytic systems are initiated by the reduction of oxidative radical precursors; the latter normally require prior preparation by tedious procedure (Scheme 1(a)) [3d]. Inspired by these work and to address the challenge above mentioned, we envisaged if our Cu(I)/chiral phosphoric acid (CPA) dual-catalysis could realize enantioselective radical-initiated 1,2-aminosilylation of alkene with hydrosilane as the reductive radical precursor in the presence of an additional commercially available and cheap oxidant. We expected a catalytic cycle wherein the silicon-centered radical would be first generated from hydrosilane through hydrogen atom abstraction (HAA) by highly reactive radical in the presence of peroxide and Cu catalyst [4]. Considering the ability of silyl group to promote the formation and stabilization of carbocation via the β-silicon effect [9], we further assumed that the *in situ* generated tertiary benzylic radical intermediate **I** might readily undergo a single-electron oxidation process in the presence of Cu^{II} species to afford a carbocation intermediate **II**. This stabilized carbocation might associate with chiral metal phosphate through electrostatic interactions [10], thereby resulting in a good chiral environment (Scheme 1(b)) for subsequent new C−N bond formation. If achieved, this type of asymmetric alkene difunctionalization strategy would be synthetically significant because the resulting chiral 1-amino-2-silylalkanes represent key structural elements of molecules widespread in medicinal chemistry and organic synthesis (Figure 1), but their asymmetric construction remains a significant challenge and point of concern [11]. Herein, we describe the development of the catalytic asymmetric radical-initiated 1,2-aminosilylation of alkene with hydrosilane enabled by Cu(I)/CPA cooperative catalysis, leading to highly enantioselective construction of skeletally diverse silicon-containing azaheterocycles including pyrrolidine, indoline and isoindoline with the creation of an α-tertiary stereocenter (Scheme 1(b)).

2 Results and discussion

Our prior observation that the use of urea as nitrogen nucleophile can provide the critical chiral environment created by the cooperative multiple hydrogen-bonding and ion-pair interactions with chiral phosphate for Cu(I)/chiral phosphoric acid (CPA)-catalyzed asymmetric alkene difunctionalization [8b] encouraged us to further select *N*-alkenyl urea **1a** as the model substrate. To do so, we initiated these investigations by examining the reaction of **1a** with $(Me_3Si)_3$-SiH (TTMSS, **2**) as the reductive radical precursor [2e] in the presence of commercially available and cheap peroxides as the oxidant catalyzed by a combination of 15 mol% of copper(I) thiophene-2-carboxylate (CuTc) and H_8-1,1′-bi-2-naphthol (BINOL)-based CPA (*R*)-**A1**. To our delight, the desired 1,2-aminosilylation product **3A** was obtained in 61% yield with 72% *ee* with lauroyl peroxide (LPO) as the external oxidant in 1,2-dimethoxyethane (DME) at 0 °C (Table 1, entry 1). Under these reaction conditions, a variety of H_8-



Scheme 1 Asymmetric radical-initiated alkene difunctionalization and aminosilylation reaction design (color online).

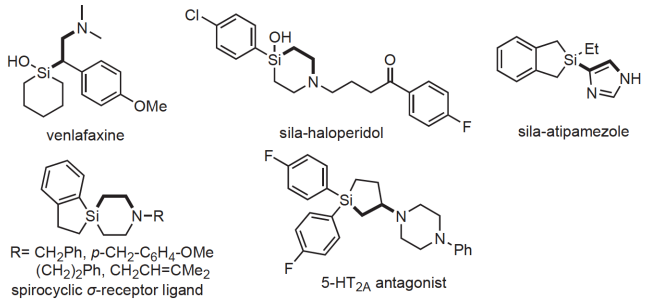
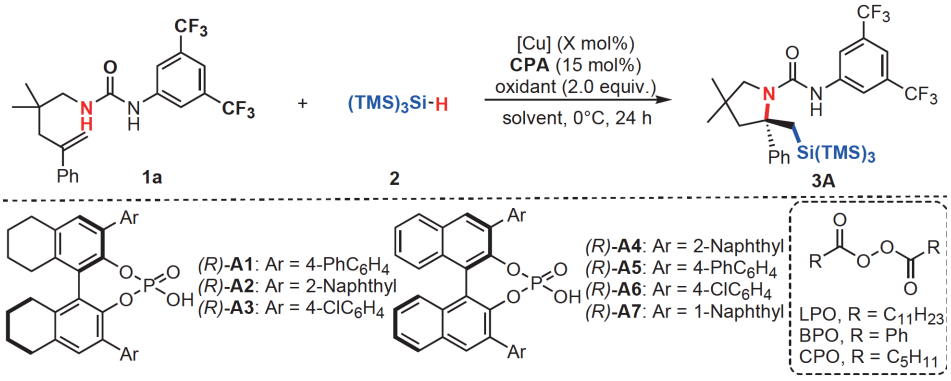


Figure 1 Representative bioactive molecules containing the key structure of 1-amino-2-silylalkanes.

BINOL- and BINOL-based CPAs were initially screened (entries 1–7) and good results (79% *ee*) were obtained using H_8-BINOL-based (*R*)-**A2** with 2-naphthyl groups at the 3,3′-positions of the backbone. To further improve enantioselectivity, we screened a series of commercially available peroxides, different copper salts and catalyst loadings as well as various organic solvents. Unfortunately, either reaction efficiency or enantioselectivity could not be significantly improved under these reaction conditions (entries 8–16). Considering the previous reports that proton-containing molecules are able to form a hydrogen bond network with

Table 1 Screening of reaction conditions [a)–c)]



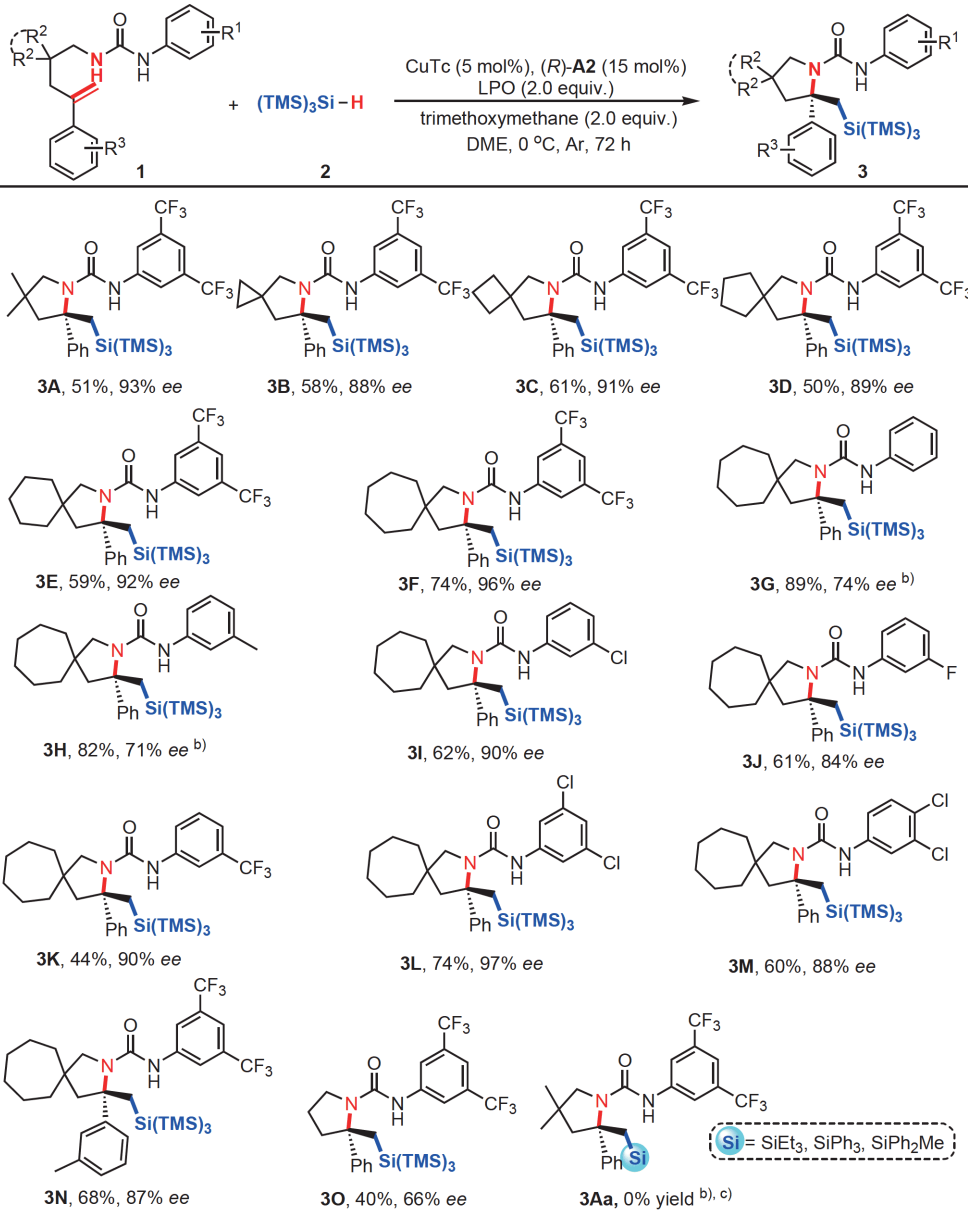
Entry	CPA	Oxidant	Solvent [l)]	Yield (%)	*ee* [m)] (%)
1	(*R*)-**A1**	LPO	DME	61	72
2	(*R*)-**A2**	LPO	DME	55	79
3	(*R*)-**A3**	LPO	DME	52	43
4	(*R*)-**A4**	LPO	DME	88	59
5	(*R*)-**A5**	LPO	DME	75	33
6	(*R*)-**A6**	LPO	DME	51	48
7	(*R*)-**A7**	LPO	DME	48	27
8 [d)]	(*R*)-**A2**	LPO	DME	84	78
9 [d)]	(*R*)-**A2**	BPO	DME	77	25
10 [d)]	(*R*)-**A2**	CPO	DME	78	72
11 [e)]	(*R*)-**A2**	LPO	DME	80	69
12 [f)]	(*R*)-**A2**	LPO	DME	82	61
13 [g)]	(*R*)-**A2**	LPO	DME	67	9
14	(*R*)-**A2**	LPO	CH_3CN	73	2
15	(*R*)-**A2**	LPO	THF	45	62
16	(*R*)-**A2**	LPO	1,4-Dioxane	75	39
17 [h)]	(*R*)-**A2**	LPO	DME	52	89
18 [i)]	(*R*)-**A2**	LPO	DME	52	82
19 [j)]	(*R*)-**A2**	LPO	DME	55	89
20 [k)]	(*R*)-**A2**	LPO	DME	54	93

a) Reaction conditions: **1a** (0.025 mmol), **2** (2 equiv.), CuTc (15 mol%), CPA (15 mol%), oxidant (2.0 equiv.), solvent (0.5 mL), 0 °C, 24 h under argon; b) yield based on ^{1}H NMR analysis of the crude product with CH_2Br_2 as an internal standard; c) *ee* value based on HPLC analysis; d) CuTc (5 mol%), 48 h under argon; e) CuCl (15 mol%); f) CuOAc (15 mol%); g) $Cu(CH_3CN)_4PF_6$ (15 mol%); h) CuTc (5 mol%), MeOH (4.0 equiv.), 72 h under argon; i) CuTc (5 mol%), EtOH (4.0 equiv.); j) CuTc (5 mol%), trimethoxymethane (4.0 equiv.); k) CuTc (5 mol%), trimethoxymethane (2.0 equiv.), 72 h under argon; l) DME=1,2-dimethoxyethane, LPO=lauroyl peroxide, BPO=benzoyl peroxide, CPO=caproyl peroxide, CuTc=copper(I) thiophene-2-carboxylate; m) *ee* is enantiomeric excess.

chiral phosphate to improve enantioselectivity [12], we then screened various alcohols and derivatives as the proton sources (entries 17–20) and found that the use of 2.0 equiv. of trimethoxymethane as the additive dramatically increased the enantioselectivity to 93% *ee* in the presence of only 5 mol% of CuTc as the catalyst.

With the optimal reaction conditions being established, we next investigated the substrate scope for the construction of chiral silicon-containing pyrrolidines (Table 2). First, a variety of cyclic *N*-alkenyl ureas containing three- to seven-membered rings within the backbone were well tolerated and provided a diverse set of enantioenriched silyl spiro products **3B**–**3F** in moderate to good yields with 88%–96% *ee*. It was also found that both the position and electronic nature of the substituents on the aromatic ring (R^1 or R^3) have a negligible effect on the reaction efficiency and stereoselectivity of the process. For example, various diversely functionalized substrates, including those having mono-substituted phenyl rings with electron-neutral (H), electron-rich (Me), or electron-deficient (F, Cl, CF_3) as well as disubstituted phenyl ring were found to be suitable substrates to afford the expected products **3G**–**3N** in 44%–89% yields with 71%–97%

Table 2 Substrate scope for the construction of pyrrolidine [a]



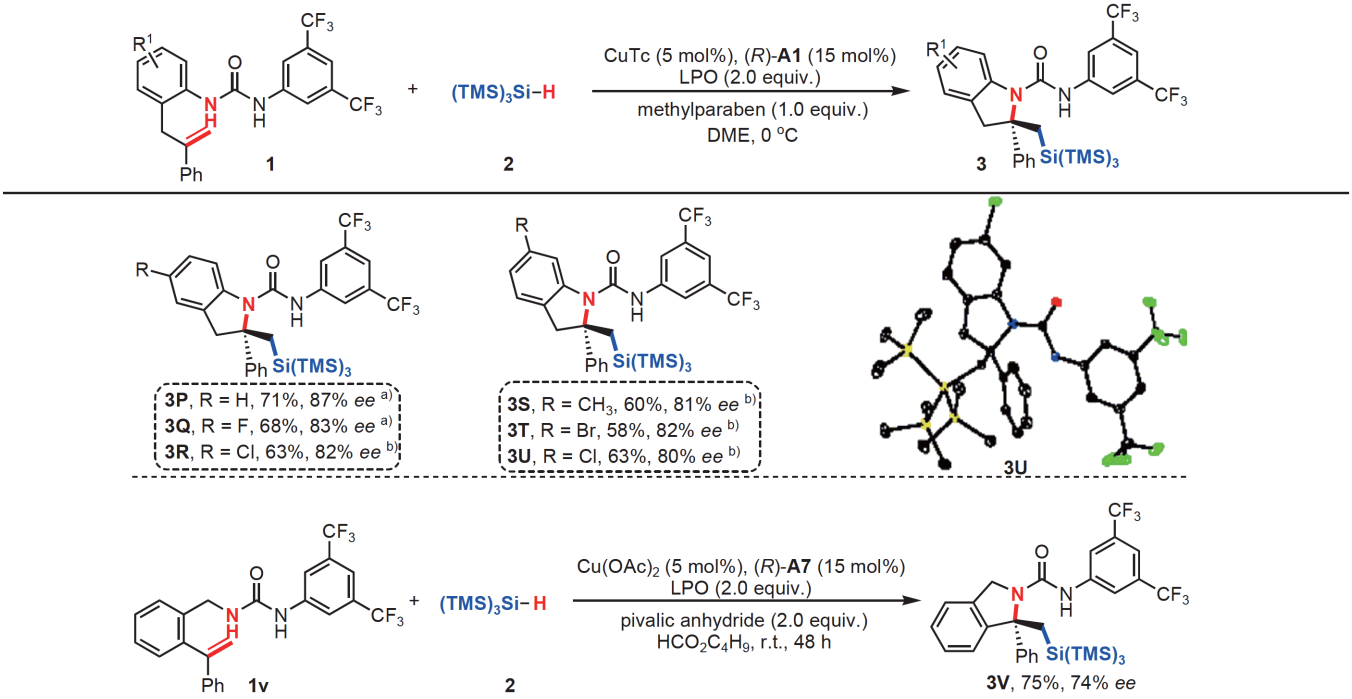
a) All of the reactions were conducted on a 0.1 mmol scale. Isolated yields based on **1** were shown. The *ee* values were determined by high performance liquid chromatography (HPLC) analysis. Reaction conditions: **1** (0.1 mmol), $(TMS)_3SiH$ (2.0 equiv.), CuTc (5 mol%), (*R*)-**A2** (15 mol%), LPO (2.0 equiv.), DME (2 mL), trimethoxymethane (2.0 equiv.), at 0 °C for 72 h under argon. b) At room temperature for 48 h under argon. c) See Supporting Information online for screening of reaction conditions.

ee. In addition, the unbranched substrate **1o** underwent the current reaction smoothly to give the corresponding product **3O** in a moderate yield with 66% *ee*. Unfortunately, other hydrosilanes are not compatible with this protocol to afford the desired aminosilylation product **3Aa** (see Table S1 in the Supporting Information online for screening of reaction conditions).

Encouraged by the aforementioned 1,2-aminosilylation with linear substrates, we next turned our attention to expand the substrate scope to 2-allylaniline derivatives, which are much less effective in our previous asymmetric difunctionalization of alkenes [8]. To our delight, upon optimizing the reaction conditions (Table S2), we identified the following protocol as optimal: 5 mol% of CuTc and 15 mol% of (*R*)-**A1** with LPO as the oxidant in the presence of methylparaben as the additive with DME as solvent at 0 °C, and the reaction of **1p** gave indoline derivative **3P** in 71% yield and 87% *ee*. Furthermore, a range of diversely functionalized 2-allylaniline derivatives, including those having electron-withdrawing and electron-donating groups at different positions of the phenyl ring within the backbone, afforded the corresponding products **3Q**–**3U** in moderate to good yields with 80%–83% *ee*. The absolute configuration of the chiral center in **3U** has been determined to be *S* by X-ray crystallographic analysis (Table 3 and Figure S1 in Supporting Information online). Meanwhile, it is striking to note that 2-vinylbenzylamine derivative could also be employed in the reaction to give isoindoline **3V** in good yield and *ee* in the presence of (*R*)-**A7** under the modified reaction conditions (Table 3). These results clearly indicate that this general asymmetric radical reaction exhibits broad substrate scope with good functional group tolerance to access skeletally diverse silicon-containing azaheterocycles including pyrrolidine, indoline and isoindline.

To exploit the synthetic application of the current method, the silylated pyrrolidine **3C** was treated with H_2O_2 (30%) and was successfully converted to chiral hydroxylated pyrrolidine **4** without great loss of *ee* value (Scheme 2, Reaction (1)). A series of control experiments were conducted to gain further insights into the reaction mechanism. First, the present reaction was completely inhibited by the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1,4-benzoquinone (BQ), and the radical trapping products $H_{23}C_{11}$-TEMPO and $(TMS)_3Si$-TEMPO were detected by gas chromatography-mass spectrometer (GC-MS). These observations indicate that the silyl radical was likely generated (Reaction (2)) [4]. In addition, no desired product **3G** was obtained in the absence of either CuTc or phosphoric acid (*R*)-**A2**, thus revealing that both the Cu(I) salt and CPA are necessary to initiate this reaction (Reaction (2)). Based on our previous results, there exist two possible pathways involving either carbocation intermediate or alkylcopper(III) intermediate to create chiral center in the reaction [8]. Actually, in our reactions, a small amount of internal alkene

Table 3 Substrate scope for the construction of indoline and isoindoline



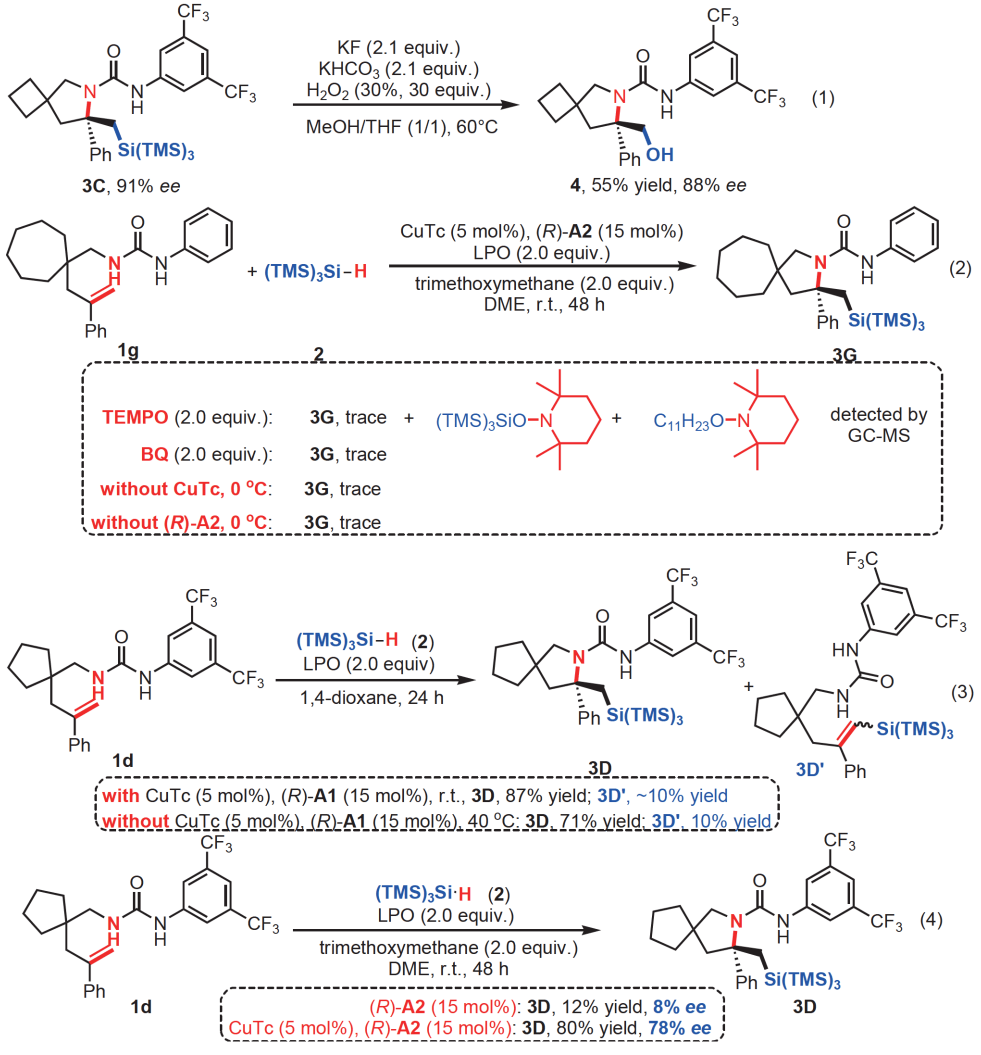
a) Reaction conditions: **1** (0.1 mmol), $(TMS)_3SiH$ (2.0 equiv.), CuTc (5 mol%), (*R*)-**A1** (15 mol%), LPO (2.0 equiv.), DME (2 mL), methylparaben (1.0 equiv), at 0 °C for 96 h under argon. b) Reaction conditions: **1** (0.1 mmol), $(TMS)_3SiH$ (2.0 equiv.), CuTc (5 mol%), (*R*)-**A1** (15 mol%), LPO (2.0 equiv.), DME (2 mL), pivalic anhydride (1.0 equiv.), at 0 °C for 96 h under argon.

product such as **3D′** was formed in some cases under the modified reaction conditions (Reaction (3)). It is possibly derived from sequential single-electron oxidation of *in situ* generated benzylic radical to form carbocation intermediate and further a β-hydrogen elimination [8h]. Furthermore, product **3D′** was also observed in 10% yield via homolysis of LPO under the thermal conditions (40 °C) in the absence of Cu/CPA catalyst (Reaction (3)). These results might possibly suggest that a carbocation intermediate **C** (structure in Scheme 3) was involved in the reaction, presumably due to the β-silicon effect to promote the formation and stabilization of carbocations [9]. In addition, the control experiment with (*R*)-**A2** as the catalyst via homolysis of LPO in the absence of the Cu catalyst furnished the desired product **3D** in only 8% *ee*. However, 78% *ee* was obtained with Cu/CPA cooperative catalysis under the same conditions, clearly indicating that Cu metal is necessary to cooperate with chiral phosphate to control asymmetric induction (Reaction (4)).

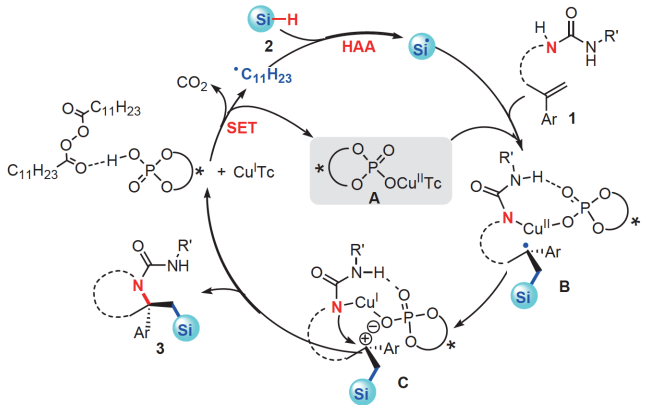
On the basis of above observations and previous reports [4,8], a plausible mechanism is tentatively proposed in Scheme 3. Initially, Cu(I) reacts with CPA-activated peroxide via heterolysis of the O–O bond followed by the loss of CO_2 to afford highly reactive alkyl radical accompanied by the crucial chiral Cu(II) phosphate complex **A** [8]. Hydrogen abstraction from **2** by alkyl radical gives the silicon-centered radical, which then adds to alkene to give alkyl radical **B**. Intramolecular single-electron oxidation of **B** with Cu(II) metal delivers the cation intermediate **C**, which could be stabilized by silyl groups at the β-position [9]. Finally, this intermediate **C** undergoes C–N bond formation invoking both hydrogen-bonding interactions and ion-pair interactions to give the final product with excellent enantioselective control.

3 Conclusions

In summary, we have developed the catalytic asymmetric radical 1,2-aminosilylation of alkene for the direct incorporation of silyl group with hydrosilane as reductive ra-



Scheme 2 Synthetic application and mechanistic study (color online).



Scheme 3 Mechanistic proposal (color online).

dical precursor under Cu(I)/CPA cooperative catalysis. This approach offers a powerful platform enabling efficient access to skeletally diverse silicon-containing azaheterocycles including pyrrolidine, indoline as well as isoindoline bearing an α-tertiary stereocenter with good efficiency and remarkable enantioselectivity. The key to success of this process relies on not only the use of Cu(I)/CPA cooperative catalyst as the single-electron reductant to realize asymmetric induction but also a silyl group to stabilize the *in situ* generated carbocation intermediate via the β-silicon effect. Further studies toward the development of a more challenging intermolecular asymmetric version are ongoing in our laboratory.

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Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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