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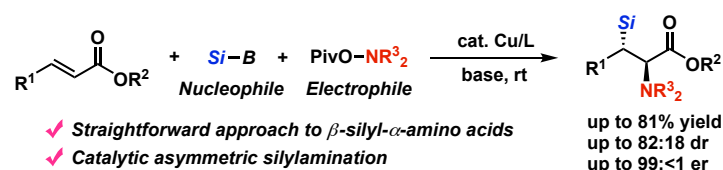
# Synthesis of $\beta$ -Silyl- $\alpha$ -amino Acid Derivatives by Cu-Catalyzed Regio- and Enantioselective Silylamination of $\alpha,\beta$ -Unsaturated Esters

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Supporting Information Placeholder



**ABSTRACT:** A copper-catalyzed silylamination of  $\alpha,\beta$ -unsaturated esters with silylboranes and hydroxylamines has been developed to afford the corresponding  $\beta$ -silyl- $\alpha$ -amino acid derivatives, which are of great interest in medicinal and pharmaceutical chemistry. Additionally, by using a suitable chiral bisphosphine ligand, the asymmetric induction is possible, delivering the optically active  $\beta$ -silyl- $\alpha$ -amino acids with synthetically acceptable diastereomeric ratios (55:45–82:18 dr) and high enantiomeric ratios (81:19–99:1 er).

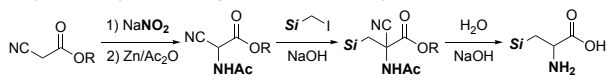
The silicon-containing  $\alpha$ -amino acids have received significant attention in medicinal chemistry because the incorporation of silicon into  $\alpha$ -amino acids can increase the solubility, metabolic stability, and lipophilicity to improve biological activities.<sup>1</sup> In particular,  $\beta$ -silyl- $\alpha$ -amino acids are important synthetic targets since significant effects of TMS-alanine were uncovered in peptidomimetic strategies.<sup>2</sup> The most common strategies for the preparation of the  $\beta$ -silyl- $\alpha$ -amino acid include the nucleophilic substitution of a glycine anion equivalent with halomethylsilanes (Scheme 1a)<sup>3</sup> and electrophilic azidation of  $\beta$ -silylesteresters using trisyl azide (Scheme 1b).<sup>4</sup> These protocols were also applied for the stereoselective synthesis using appropriate chiral auxiliaries.<sup>5</sup> On the other hand, Piersanti, Shi, and Zhang recently reported alternative strategies based on the silylation reaction of  $\alpha$ -amino acid derivatives: copper-catalyzed silyl-conjugate additions to dehydroalanine derivatives from serine (Scheme 1c, top)<sup>6</sup> and palladium-catalyzed C-H silylation of alanine derivatives (Scheme 1c, bottom).<sup>7</sup> Additionally, the related pericyclic reaction approaches were developed.<sup>8</sup> Despite the aforementioned certain progress, there are still some disadvantages: only the alanine-type products are accessible (Scheme 1a and 1c, top); strong bases such as LDA (Scheme 1b) and high temperature (Scheme 1c, bottom) are inevitable; and tedious NO<sub>2</sub>/N<sub>3</sub> reduction (Schemes 1a and 1b) and attachment/detachment of the aminoquinoline directing group (Q; Scheme 1c, bottom) are necessary. Moreover, the diastereoselectivity is well controlled in several strate-

gies,<sup>4,7</sup> but the catalytic enantiocontrolled process still remains a challenge. Therefore, it is highly desirable to develop a more practical and straightforward method to prepare the  $\beta$ -silyl- $\alpha$ -amino acids.

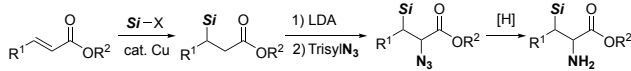
Herein, we report a new protocol for the simultaneous addition of silyl and amino groups to the  $\alpha,\beta$ -unsaturated esters in a catalytic manner: copper-catalyzed silylamination with silylboranes<sup>9</sup> and hydroxylamines is described (Scheme 1d, top). The  $\beta$ -silyl- $\alpha$ -amino acid derivatives can be directly prepared with 55:45–82:18 diastereoselectivity in one synthetic operation from the readily available and simple acrylates. Our strategy is based on an umpolung, electrophilic amination:<sup>10</sup> the silylborane and the hydroxylamine act as the silyl nucleophile and the amino electrophile, respectively, and add at the  $\beta$ - and  $\alpha$ -position of the  $\alpha,\beta$ -unsaturated ester regioselectively. Thus, the targeted  $\beta$ -silyl- $\alpha$ -amino acids are selectively obtained, which is difficult to achieve under conventional silylamination conditions using silylamines<sup>11</sup> or parent amines<sup>12</sup> owing to the Michael acceptor character of  $\alpha,\beta$ -unsaturated esters. Furthermore, a judicious choice of ancillary chiral bisphosphine ligand renders the reaction enantioselective, and optically active  $\beta$ -silyl- $\alpha$ -amino acid derivatives are formed with high enantioselectivity (81:19–99:1 er). To the best of our knowledge, the successful use of the silyl nucleophile in the electrophilic amination system is unprecedented in the literature. Additionally, this is one of the limited successful examples of the asymmetric silylamination of alkenes.<sup>12c</sup>

## Scheme 1. Synthetic Strategies of $\beta$ -Silyl- $\alpha$ -amino Acid Derivatives

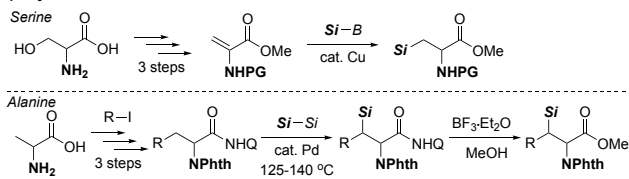
### a) Alkylation of Glycine Anion Equivalent with Halomethylsilanes



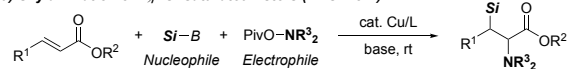
### b) Electrophilic Azidation of $\beta$ -Silylestere



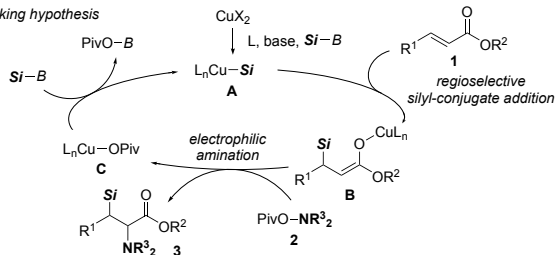
### c) Silylation of $\alpha$ -Amino Acid Derivatives



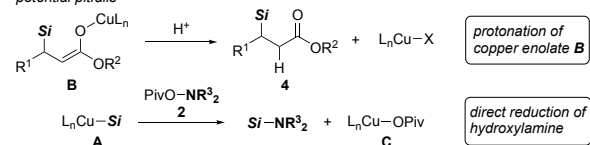
### d) Silylamination of $\alpha,\beta$ -Unsaturated Esters (This Work)



#### working hypothesis



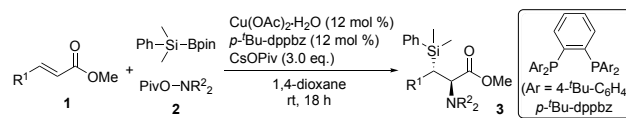
#### potential pitfalls



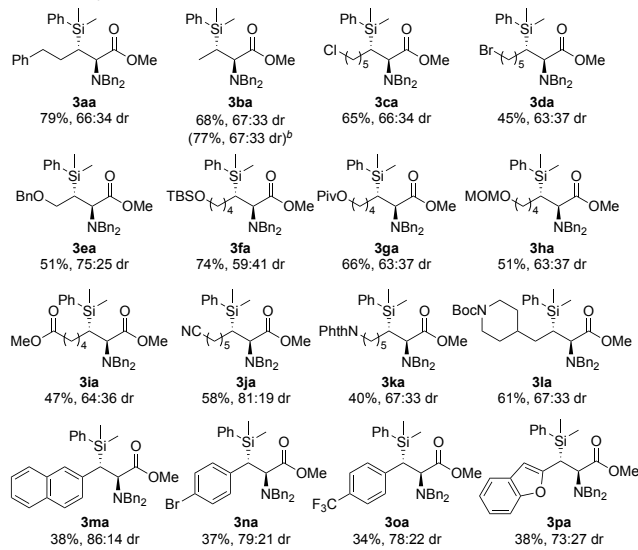
Our working hypothesis is shown in Scheme 1d (middle). The initial step is the generation of a catalytically active  $L_n\text{Cu-Si}$  species **A** from a starting copper salt  $\text{CuX}_2$ , a supporting ligand *L*, and a silylborane *Si-B* by the action of an external base. Subsequent 1,4-addition with the  $\alpha,\beta$ -unsaturated ester **1** affords the  $\beta$ -silylated *O*-bound copper enolate **B**, which then undergoes the electrophilic amination with the *O*-pivaloylhydroxylamine **2**.<sup>13</sup> The successful C–N bond formation at the  $\alpha$ -position to carbonyl produces the desired  $\beta$ -silyl- $\alpha$ -amino acid derivative **3** along with the copper pivalate **C**. The catalytic cycle is closed by metathesis between **C** and the silylborane *Si-B*. The catalytic generation and the use of silylmetal species via  $\sigma$ -bond metathesis with the silylborane reagent were originally reported by Oestreich and subsequently developed by many researchers.<sup>14</sup> The electrophilic amination of organocopper species was also studied by some research groups.<sup>10</sup> However, there are two potential pitfalls (Scheme 1d, bottom). One is the rapid protonation of copper enolate **B** to form the hydrosilylated product **4**. Actually, the copper-catalyzed silyl-conjugate additions to  $\alpha,\beta$ -unsaturated carbonyl compounds were reported, but the tandem functionalization at the  $\alpha$  position still remains a challenge, except for a few successful examples of the aldol-type reaction.<sup>15</sup> Therefore, suppression of the undesired protonation is the most important task for the devel-

opment of the silylamination reaction. Another conceivable side reaction is the nonproductive decomposition of the hydroxylamine **2** through the silylative N–O bond cleavage with the silylcopper **A**. Namely, even in the presence of the hydroxylamine, the silylcopper **A** is required to react with the unsaturated ester **1** much more readily.

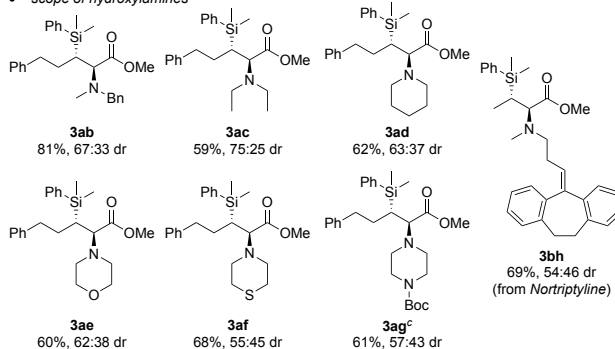
## Scheme 2. Copper-Catalyzed Silylamination of $\alpha,\beta$ -Unsaturated Esters **1** with $\text{PhMe}_2\text{Si-Bpin}$ and Hydroxylamines **2**<sup>a</sup>



#### scope of $\alpha,\beta$ -unsaturated esters



#### scope of hydroxylamines



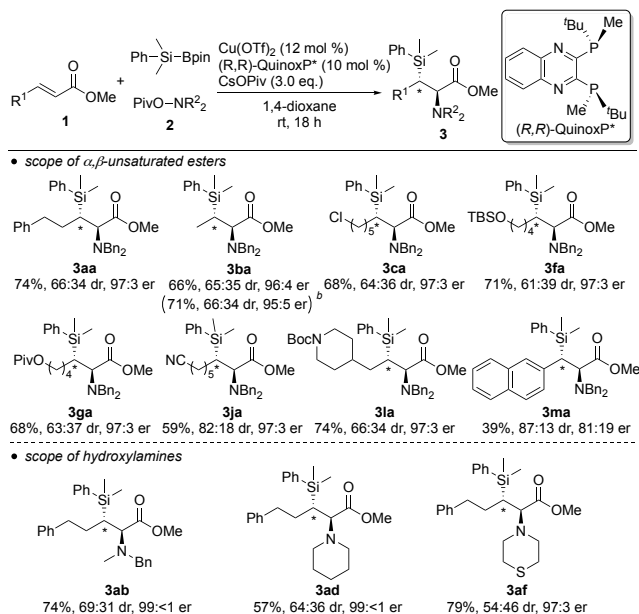
<sup>a</sup>Conditions: **1** (0.50 mmol),  $\text{PhMe}_2\text{Si-Bpin}$  (0.63 mmol), **2** (0.25 mmol),  $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$  (0.030 mmol), *p*-Bu-dppbz (0.030 mmol), CsOPiv (0.75 mmol), 1,4-dioxane (1.0 mL), rt, 18 h,  $\text{N}_2$ . Isolated yields are shown. <sup>b</sup>On 1.0 mmol scale. <sup>c</sup>With *O*-benzoylhydroxylamine.

Optimization studies commenced with methyl (*E*)-5-phenylpent-2-enoate (**1a**),  $\text{PhMe}_2\text{Si-Bpin}$ , and *O*-pivaloyl-*N,N*-dibenzylhydroxylamine (**2a**) as model substrates (Scheme 2). After the extensive screening of various reaction parameters, we found that the reaction proceeded in the presence of the  $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}/p\text{-Bu-dppbz}$  catalyst and a CsOPiv base to form the targeted  $\beta$ -silyl- $\alpha$ -amino acid **3aa** in 79% yield with 66:34 *anti/syn* diastereomeric ratio. Some observations are to be noted: CsOPiv increased the product selectivity over the hydrosilylated

byproduct. The choice of ligand was critical, and *p*-*t*-Bu-dppbz accelerated the silyl conjugate addition beyond the conceivable nonproductive N–O bond cleavage of the hydroxylamine. The moderate dr was kinetically determined, and no epimerization of product occurred under the optimal conditions (see the Supporting Information for more details). With the optimal conditions in hand, we investigated the substrate scope of the copper-catalyzed silylamination. The reaction was compatible with various functional groups including alkyl chloride, alkyl bromide, benzyl ether, silyl ether, pivaloyl ester, acetal, methyl ester, nitrile, phthalimide, and Boc-protected amine to deliver the target  $\beta$ -silyl- $\alpha$ -amino acid derivatives **3ca–1a** in moderate to good yields. Additionally, several cinamates could also be employed albeit with slightly lower efficiency (**3ma–3pa**). The scope of the hydroxylamine was also substantially broad: *N*-benzyl-*N*-methylamine, *N,N*-diethylamine, piperidine, morpholine, thiomorpholine, and piperazine all were successfully coupled with **1a** to afford the corresponding  $\beta$ -silyl- $\alpha$ -amino acids **3ab–ag** in 59–81% yields, regardless of its cyclic or acyclic structure. Particularly notable is the successful coupling with the antidepressant, nortriptyline (**3bh**). Furthermore, the reaction was conducted on a 1.0 mmol scale without any difficulty (**3ba**), indicating the scalability and reproducibility of the copper catalysis.

Our next target was the enantioenriched  $\beta$ -silyl- $\alpha$ -amino acid by the enantioselective silylamination. According to the scenario in Scheme 1d, the appropriate choice of the chiral ligand can induce the enantioselectivity at the 1,4-addition step (**A** to **B**) and/or the C–N bond forming step (**B** to **3**). After the evaluation of chiral ligands, we were pleased to find that the optically active **3aa** was obtained from **1a** and **2a** in 74% isolated yield with 97:3 enantiomeric ratio (er) under the Cu(OTf)<sub>2</sub>/(*R,R*)-QuinoxP\* catalysis<sup>16</sup> (Scheme 3). The enantioselective reaction could also be performed on a 1.0 mmol scale (**3ba**). The absolute configuration was assigned by comparison of the HPLC chart with the known compound after the derivatization. Considering that the hydrosilylated byproduct **4b** was also formed with a high enantiomeric ratio, the chirality at the  $\beta$ -position is well controlled by the chiral copper catalyst in the silyl-conjugate addition step (Scheme 1d, **A** to **B**), but the stereoselectivity at the  $\alpha$ -position was negligibly induced in the electrophilic amination step (Scheme 1d, **B** to **3**), thus leading to the observed moderate diastereomeric ratio. However, both *anti* and *syn* diastereomers could be separated from each other after the exchange of the protecting group on nitrogen (see the Supporting Information for details). The asymmetric catalysis was also tolerant of the alkyl chloride, silyl ether, pivaloyl ester, nitrile, and Boc-protected amine moieties, and the corresponding functionalized chiral  $\beta$ -silyl- $\alpha$ -amino acids **3ca**, **fa**, **ga**, **ja**, and **1a** were formed in good yields with 97:3 er. Methyl 2-naphthyl acrylate **1m** was also amenable to the asymmetric silylamination with acceptable enantioselectivity. In addition to **2a**, *N*-benzyl-*N*-methylamine, piperidine, and thiomorpholine worked well to deliver the target chiral  $\beta$ -silyl- $\alpha$ -amino acids **3ab**, **ad**, and **af** with high enantioselectivity.

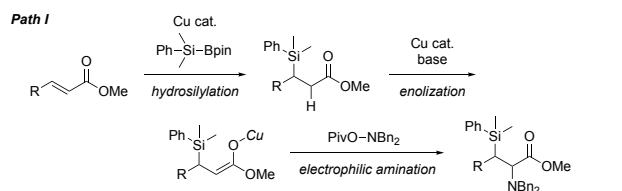
### Scheme 3. Copper-Catalyzed Enantioselective Silylamination of $\alpha,\beta$ -Unsaturated Esters **1** with PhMe<sub>2</sub>Si-Bpin and Hydroxylamines **2**<sup>a</sup>



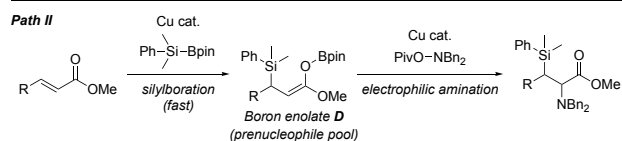
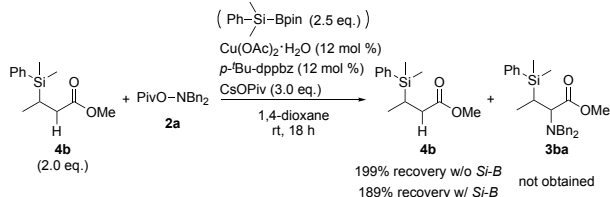
<sup>a</sup>Conditions: **1** (0.50 mmol), PhMe<sub>2</sub>Si-Bpin (0.63 mmol), **2** (0.25 mmol), Cu(OTf)<sub>2</sub> (0.030 mmol), QuinoxP\* (0.025 mmol), CsOPiv (0.75 mmol), 1,4-dioxane (1.0 mL), rt, 18 h, N<sub>2</sub>. Isolated yields are shown. <sup>b</sup>On a 1.0 mmol scale.

We then performed some mechanistic studies. In Scheme 1d, the  $\alpha,\beta$ -unsaturated ester **1** undergoes the silyl-conjugate addition reaction, and the formed *O*-bound copper enolate **B** directly enters the C–N bond forming step with the hydroxylamine **2**. However, there are two other possibilities. One is a stepwise pathway, including conjugate hydrosilylation, enolization, and electrophilic amination (Scheme 4, Path I). Actually, the hydrosilylated product **4** was observed as the major byproduct under the optimized conditions. However, upon exposure of the independently prepared **4b** into otherwise identical conditions, the aminated product **3ba** was not detected at all, and the starting **4b** was recovered almost quantitatively. The additional use of PhMe<sub>2</sub>Si-Bpin also resulted in no formation of **3ba**, thus excluding the possibility of Path I. Another is the silylboration/electrophilic amination (Scheme 4, Path II). The copper-catalyzed silylboration proceeds fast, and the pre-nucleophile pool, boron enolate **D**,<sup>14e</sup> then undergoes the copper-catalyzed electrophilic amination. To investigate this possibility, we monitored a reaction mixture of **1b**, PhMe<sub>2</sub>Si-Bpin, and **2a** by <sup>1</sup>H NMR in 1,4-dioxane-*d*<sub>8</sub>. If the boron enolate **D** is accumulated predominantly, the acrylate **1b** is rapidly consumed, and the aminated product **3ba** is then gradually generated. However, the aminated product **3ba** was formed promptly alongside the decrease of acrylate **1b**. We also confirmed no clear formation of the boron enolate **D** by the reaction of **1a** and PhMe<sub>2</sub>Si-Bpin without **2a** (see the Supporting Information for details). To gain more solid support, the reactivity of the boron enolate **D** was also independently examined. According to the reported procedure,<sup>17</sup> the boron enolate **5b** was generated *in situ* and then added to a mixture of the copper catalyst and **2a**. The aminated product **6ba** was observed in only 2% yield, and the protonated product was obtained mainly. The addition of CsOPiv also gave a similar result even in C<sub>6</sub>D<sub>6</sub>/1,4-dioxane-*d*<sub>8</sub> mixed solvent system. These findings suggest

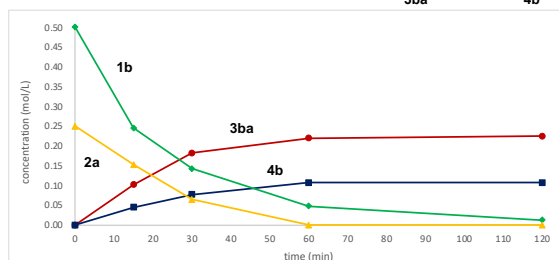
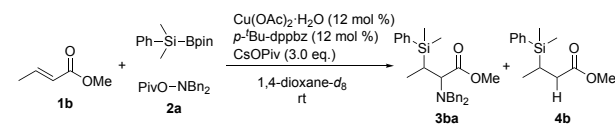
## Scheme 4. Other Possible Pathways and Evaluation of Potential Intermediates



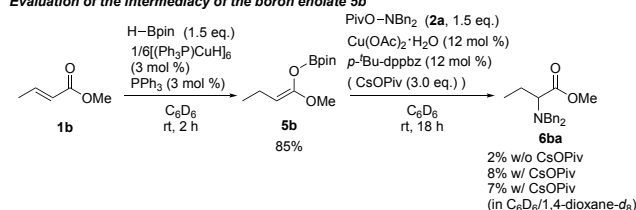
### Evaluation of the intermediacy of the hydro-silylated product 4b



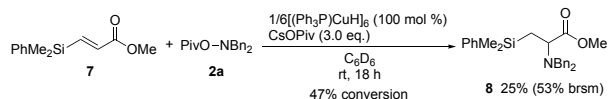
### Monitoring study of reaction mixture



### Evaluation of the intermediacy of the boron enolate 5b



### Stoichiometric reaction under borane-free conditions



that the boron enolate **D** is basically converted to the protonated byproduct under optimal conditions, even if it is formed. Namely, Path II is also unlikely, and the originally proposed C–N bond forming pathway in Scheme 1d is the most favorable. Actually, the  $\beta$ -silyl- $\alpha$ -aminosilane **8** was formed from stoichiometric amounts of  $[(\text{Ph}_3\text{P})\text{CuH}]_6$ ,  $\beta$ -silyl- $\alpha,\beta$ -unsaturated ester **7**, and hydroxylamine **2a** even under the borane-free conditions.

In conclusion, we have developed a copper-catalyzed silylamination of  $\alpha,\beta$ -unsaturated esters with silylboranes and *O*-pivaloylhydroxylamines to form the corresponding  $\beta$ -silyl- $\alpha$ -amino acid derivatives. Additionally, the asymmetric induction is possible by using the suitable chiral

bisphosphine ligand. The asymmetric copper catalysis can provide more straightforward access to the optically active  $\beta$ -silyl- $\alpha$ -amino acids of high potential in medicinal chemistry. Further manipulation of products, improvement of diastereoselectivity,<sup>18</sup> and more detailed mechanistic studies are ongoing in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxx.

<sup>1</sup>H, <sup>13</sup>C{<sup>1</sup>H}, and <sup>19</sup>F{<sup>1</sup>H} NMR spectra, characterization data, stereochemical assignment, detailed optimization studies, experimental procedures, substrate limitation, control experiments, and discussion about the role of base (PDF)

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### Author Contributions

†T.K. and S.N. contributed equally to this work.

### Notes

The authors declare no competing financial interest.

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## REFERENCES

- (1) For selected reviews, see: (a) Mortensen, M.; Husmann, R.; Veri, E.; Bolm, C. Synthesis and applications of silicon-containing  $\alpha$ -amino acids. *Chem. Soc. Rev.* **2009**, *38*, 1002-1010. (b) Franz, A. K.; Wilson, S. O. Organosilicon Molecules with Medicinal Applications. *J. Med. Chem.* **2013**, *56*, 388-405. (c) Rémond, E.; Martin, C.; Martinez, J.; Cavellier, F. Silicon-Containing Amino Acids: Synthetic Aspects, Conformational Studies, and Applications to Bioactive Peptides. *Chem. Rev.* **2016**, *116*, 11654-11684. (d) Ramesh, R.; Reddy, D. S. Quest for Novel Chemical Entities through Incorporation of Silicon in Drug Scaffolds. *J. Med. Chem.* **2018**, *61*, 3779-3798.

- (2) Tacke, R.; Merget, M.; Bertermann, R.; Bernd, M.; Beckers, T.; Reissmann, T. Syntheses and Properties of Silicon- and Germanium-Containing  $\alpha$ -Amino Acids and Peptides: A Study on C/Si/Ge Bioisosterism. *Organometallics* **2000**, *19*, 3486-3497.
- (3) Birkofer, L.; Ritter, A. Silicoamino Acids and Silazane-carboxylic Acid Esters. *Angew. Chem.* **1956**, *68*, 461-462.
- (4) Panek, J. S.; Beresis, R.; Xu, F.; Yang, M. Diastereoselective Electrophilic Addition Reactions to Chiral  $\beta$ -Dimethylphenylsilyl Ester Enolates. Synthesis of 2,3-Anti- $\alpha$ -substituted- $\beta$ -silyl-(E)-hex-4-enoates. *J. Org. Chem.* **1991**, *56*, 7341-7344.
- (5) (a) Fitz, R.; Seebach, D. Resolution and Use in  $\alpha$ -Amino Acid Synthesis of Imidazolidinone Glycine Derivatives. *Tetrahedron* **1988**, *44*, 5277-5292. (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. Highly Practical Methodology for the Synthesis of D- and L- $\alpha$ -Amino Acids, N-Protected  $\alpha$ -Amino Acids, and N-Methyl- $\alpha$ -Amino Acids. *J. Am. Chem. Soc.* **1997**, *119*, 656-673. (c) Walkup, R. D.; Cole, D. C.; Whittlesey, B. R. Silicon-Containing Amino Acids and Peptides. Asymmetric Synthesis of (Trialkylsilyl)-Alanines. *J. Org. Chem.* **1995**, *60*, 2630-2634.
- (6) Bartocchini, F.; Bartolucci, S.; Lucarini, S.; Piersanti, G. Synthesis of Boron- and Silicon-Containing Amino Acids through Copper-Catalyzed Conjugate Additions to Dehydroalanine Derivatives. *Eur. J. Org. Chem.* **2015**, *2015*, 3352-3360.
- (7) (a) Liu, Y.-J.; Liu, Y.-H.; Zhang, Z.-Z.; Yan, S.-Y.; Chen, K.; Shi, B.-F. Divergent and Stereoselective Synthesis of  $\beta$ -Silyl- $\alpha$ -Amino Acids through Palladium-Catalyzed Intermolecular Silylation of Unactivated Primary and Secondary C-H Bonds. *Angew. Chem., Int. Ed.* **2016**, *55*, 13859-13862. (b) Pan, J.-L.; Li, Q.-Z.; Zhang, T.-Y.; Hou, S.-H.; Kang, J.-C.; Zhang, S.-Y. Palladium-catalyzed direct intermolecular silylation of remote unactivated C(sp<sup>3</sup>)-H bonds. *Chem. Commun.* **2016**, *52*, 13151-13154.
- (8) Zhang, C.; Ito, H.; Maeda, Y.; Shirai, N.; Ikeda, S.; Sato, Y. Novel Isomerization Reaction of N,N-Dimethyl- $\alpha$ -(methoxycarbonyl)-4-substituted-benzylammonium N-Methylides. *J. Org. Chem.* **1999**, *64*, 581-586. See the Supporting Information for a complete list of references.
- (9) For selected reviews, see: (a) Ohmura, T.; Suginome, M. Silylboranes as New Tools in Organic Synthesis. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29-49. (b) Oestreich, M.; Hartmann, E.; Mewald, M. Activation of the Si-B Interelement Bond: Mechanism, Catalysis, and Synthesis. *Chem. Rev.* **2013**, *113*, 402-441. (c) Xue, W.; Oestreich, M. Beyond Carbon: Enantioselective and Enantiospecific Reactions with Catalytically Generated Boryl- and Silylcopper Intermediates. *ACS Cent. Sci.* **2020**, *6*, 1070-1081. (d) Feng, J.-J.; Mao, W.; Zhang, L.; Oestreich, M. Activation of the Si-B interelement bond related to catalysis. *Chem. Soc. Rev.* **2021**, *50*, 2010-2073.
- (10) For related seminal work on electrophilic amination with hydroxylamines, see: (a) Tsutsui, H.; Hayashi, Y.; Narasaka, K. Preparation of Primary Amines by the Copper(I) Catalyzed Reaction of 4,4'-Bis(trifluoromethyl)benzophenone O-Methylsulfonyloxime and Alkyl Grignard Reagents. *Chem. Lett.* **1997**, *26*, 317-318. (b) Berman, A. M.; Johnson, J. S. Copper-Catalyzed Electrophilic Amination of Diorganozinc Reagents. *J. Am. Chem. Soc.* **2004**, *126*, 5680-5681. For recent reviews and perspectives, see: (c) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. Copper Hydride Catalyzed Hydroamination of Alkenes and Alkynes. *Angew. Chem., Int. Ed.* **2016**, *55*, 48-57. (d) Hirano, K.; Miura, M. Hydroamination, Aminoboration, and Carboamination with Electrophilic Amination Reagents: Umpolung-Enabled Regio- and Stereoselective Synthesis of N-Containing Molecules from Alkenes and Alkynes. *J. Am. Chem. Soc.* **2022**, *144*, 648-661. See the Supporting Information for a complete list of references.
- (11) Hojo, M.; Nagayoshi, M.; Fujii, A.; Yanagi, T.; Ishibashi, N.; Miura, K.; Hosomi, A. Introduction of Electrophiles to the  $\alpha$ -Position of  $\alpha,\beta$ -Unsaturated Aldehydes and Ketones by Sequential Conjugate Aminosilylation-Alkylation-Deamination. *Chem. Lett.* **1994**, *23*, 719-722.
- (12) (a) Yang, Y.; Song, R.-J.; Ouyang, X.-H.; Wang, C.-Y.; Li, J.-H.; Luo, S. Iron-Catalyzed Intermolecular 1,2-Difunctionalization of Styrenes and Conjugated Alkenes with Silanes and Nucleophiles. *Angew. Chem., Int. Ed.* **2017**, *56*, 7916-7919. (b) Torii, K.; Kawakubo, A.; Lin, X.; Fujihara, T.; Yajima, T.; Obora, Y. Palladium-Catalyzed Difunctionalization of 1,3-Diene with Amine and Disilane under a Mild Re-oxidation System. *Chem. - Eur. J.* **2021**, *27*, 4888-4892. (c) Zeng, Y.; Liu, X.-D.; Guo, X.-Q.; Gu, Q.-S.; Li, Z.-L.; Chang, X.-Y.; Liu, X.-Y. Cu/chiral phosphoric acid-catalyzed radical-initiated asymmetric aminosilylation of alkene with hydrosilane. *Sci. China Chem.* **2019**, *62*, 1529-1536.
- (13) For recent computational studies on the electrophilic amination of organocopper species with the hydroxylamine, see: Tobisch, S. CuH-Catalysed Hydroamination of Styrene with Hydroxylamine Esters: A Coupled Cluster Scrutiny of Mechanistic Pathways. *Chem. - Eur. J.* **2016**, *22*, 8290-8300.
- (14) For the pioneering work by Oestreich, see: (a) Walter, C.; Oestreich, M. Catalytic Asymmetric C-Si Bond Formation to Acyclic  $\alpha,\beta$ -Unsaturated Acceptors by Rh<sup>I</sup>-Catalyzed Conjugate Silyl Transfer Using a Si-B Linkage. *Angew. Chem., Int. Ed.* **2008**, *47*, 3818. For reviews, see: (b) Hartmann, E.; Vyas, D. J.; Oestreich, M. Enantioselective formal hydration of  $\alpha,\beta$ -unsaturated acceptors: asymmetric conjugate addition of silicon and boron nucleophiles. *Chem. Commun.* **2011**, *47*, 7917-7932. (c) Fujihara, T.; Tsuji, Y. Cu-Catalyzed Borylative and Silylative Transformations of Allenes: Use of  $\beta$ -Functionalized Allyl Copper Intermediates in Organic Synthesis. *Synthesis* **2018**, *50*, 1737-1749. Recent selected publications: (d) Lee, K.-s.; Hoveyda, A. H. Enantioselective Conjugate Silyl Additions to Cyclic and Acyclic Unsaturated Carbonyls Catalyzed by Cu Complexes of Chiral N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2010**, *132*, 2898-2900. (e) O'Brien, J. M.; Hoveyda, A. H. Metal-Free Catalytic C-Si Bond Formation in an Aqueous Medium. Enantioselective NHC-Catalyzed Silyl Conjugate Additions to Cyclic and Acyclic  $\alpha,\beta$ -Unsaturated Carbonyls. *J. Am. Chem. Soc.* **2011**, *133*, 7712-7715. (f) Calderone, J. A.; Santos, W. L. Copper(II)-Catalyzed Silyl Conjugate Addition to  $\alpha,\beta$ -Unsaturated Conjugated Compounds: Brønsted Base-Assisted Activation of Si-B Bond in Water. *Org. Lett.* **2012**, *14*, 2090-2093. (g) Mao, W.; Oestreich, M. Enantioselective Synthesis of  $\alpha$ -Chiral Propargylic Silanes by Copper-Catalyzed 1,4-Selective Addition of Silicon Nucleophiles to Enyne-Type  $\alpha,\beta,\gamma,\delta$ -Unsaturated Acceptors. *Org. Lett.* **2020**, *22*, 8096-8100.
- (15) For some related papers on the three-component coupling aldol-type reactions using  $\alpha,\beta$ -unsaturated carbonyl compounds, silylboranes, and electrophiles: (a) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. Catalytic enantioselective intermolecular reductive aldol reaction to ketones. *Tetrahedron Lett.* **2006**, *47*, 1403-1407. (b) Welle, A.; Petriguet, J.; Tinant, B.; Wouters, J.; Riant, O. Copper-Catalysed Domino Silylative Aldol Reaction Leading to Stereocontrolled Chiral Quaternary Carbons. *Chem. - Eur. J.* **2010**, *16*, 10980-10983. (c) Welle, A.; Cirriez, V.; Riant, O. Copper catalyzed tandem conjugated borylation - aldol reaction. *Tetrahedron* **2012**, *68*, 3435-3443. (d) Zhang, L.; Oestreich, M. Diastereotopic Group-Selective Intramolecular Aldol Reactions Initiated by Enantioselective Conjugate Silylation: Diastereodivergence Controlled by the Silicon Nucleophile. *ACS Catal.* **2021**, *11*, 3516-3522.
- (16) For application of QuinoxP\* in catalysis, see: (a) Imamoto, T.; Sugita, K.; Yoshida, K. An Air-Stable P-Chiral Phosphine Ligand for Highly Enantioselective Transition-Metal-Catalyzed Reactions. *J. Am. Chem. Soc.* **2005**, *127*, 11934-11935. (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. Copper-Catalyzed Enantioselective Substitution of Allylic Carbonates with Diboron: An Efficient Route to Optically Active  $\alpha$ -Chiral Allylboronates. *J. Am. Chem. Soc.* **2007**, *129*, 14856-14857.
- (17) Ng, E. W. H.; Low, K.-H.; Chiu, P. Synthesis and Applications of Unquaternized C-Bound Boron Enolates. *J. Am. Chem. Soc.* **2018**, *140*, 3537-3541.
- (18) See the Supporting Information for preliminary attempts to improve diastereoselectivity by nitrile additives.

