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Synthesis of *β*-Silyl-*α*-amino Acid Derivatives by Cu-Catalyzed Regio- and Enantioselective Silylamination of *α,β*-Unsaturated Esters

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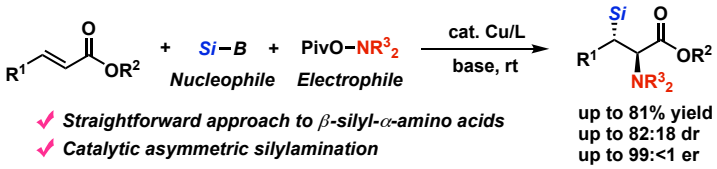
Supporting Information Placeholder

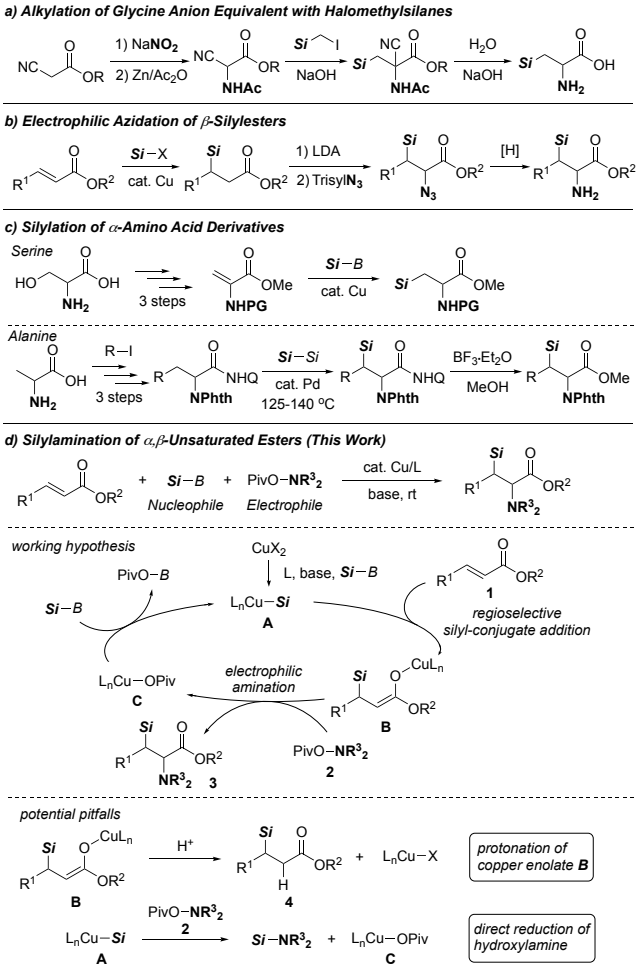


ABSTRACT: A copper-catalyzed silylamination of *α,β*-unsaturated esters with silylboranes and hydroxylamines has been developed to afford the corresponding *β*-silyl-*α*-amino acid derivatives, which are of great interest in medicinal and pharmaceutical chemistry. Additionally, by using a suitable chiral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

The silicon-containing *α*-amino acids have received significant attention in medicinal chemistry because the incorporation of silicon into *α*-amino acids can increase the solubility, metabolic stability, and lipophilicity to improve biological activities.[1] In particular, *β*-silyl-*α*-amino acids are important synthetic targets since significant effects of TMS-alanine were uncovered in peptidomimetic strategies.[2] The most common strategies for the preparation of the *β*-silyl-*α*-amino acid include the nucleophilic substitution of a glycine anion equivalent with halomethylsilanes (Scheme 1a)[3] and electrophilic azidation of *β*-silylesters using trisyl azide (Scheme 1b).[4] These protocols were also applied for the stereoselective synthesis using appropriate chiral auxiliaries.[5] On the other hand, Piersanti, Shi, and Zhang recently reported alternative strategies based on the silylation reaction of *α*-amino acid derivatives: copper-catalyzed silyl-conjugate additions to dehydroalanine derivatives from serine (Scheme 1c, top)[6] and palladium-catalyzed C-H silylation of alanine derivatives (Scheme 1c, bottom).[7] Additionally, the related pericyclic reaction approaches were developed.[8] 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_2/N_3 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 strategies,[4,7] 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 *β*-silyl-*α*-amino acids.

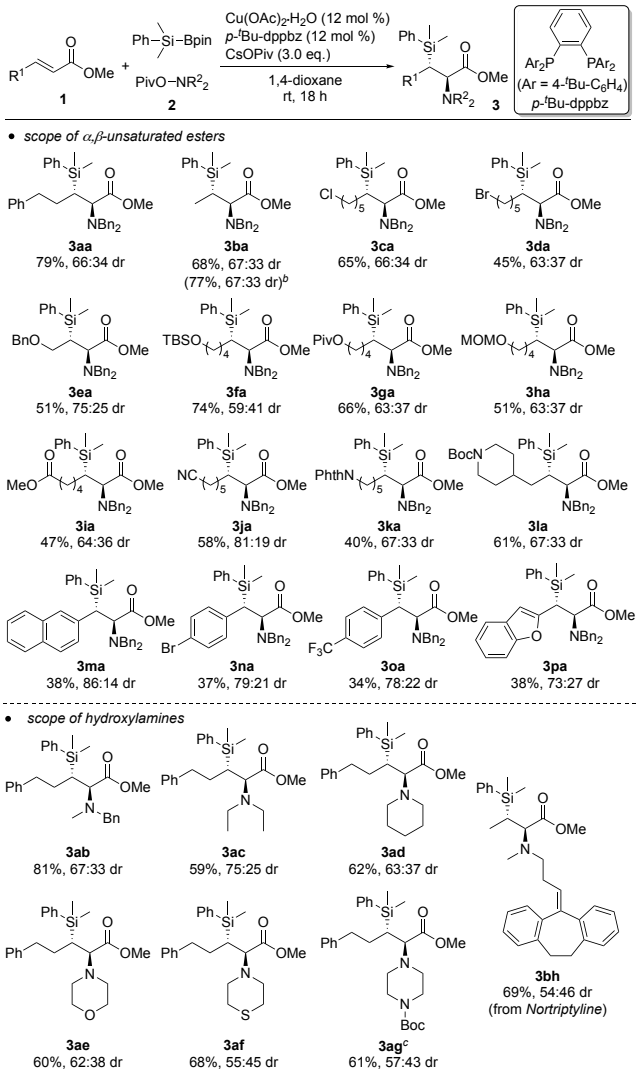
Herein, we report a new protocol for the simultaneous addition of silyl and amino groups to the *α,β*-unsaturated esters in a catalytic manner: copper-catalyzed silylamination with silylboranes[9] and hydroxylamines is described (Scheme 1d, top). The *β*-silyl-*α*-amino acid derivatives can be directly 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:[10] the silylborane and the hydroxylamine act as the silyl nucleophile and the amino electrophile, respectively, and add at the β- and α-position of the *α,β*-unsaturated ester regioselectively. Thus, the targeted *β*-silyl-*α*-amino acids are selectively obtained, which is difficult to achieve under conventional silylamination conditions using silylamines[11] or parent amines[12] owing to the Michael acceptor character of *α,β*-unsaturated esters. Furthermore, a judicious choice of ancillary chiral bisphosphine ligand renders the reaction enantioselective, and optically active *β*-silyl-*α*-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.[12c]

Scheme 1. Synthetic Strategies of *β*-Silyl-*α*-amino Acid Derivatives



Our working hypothesis is shown in Scheme 1d (middle). The initial step is the generation of a catalytically active L_nCu–Si species **A** from a starting copper salt CuX_2, a supporting ligand L, and a silylborane Si-B by the action of an external base. Subsequent 1,4-addition with the *α,β*-unsaturated ester **1** affords the *β*-silylated *O*-bound copper enolate **B**, which then undergoes the electrophilic amination with the *O*-pivaloylhydroxylamine **2**.[13] The successful C–N bond formation at the α-position to carbonyl produces the desired *β*-silyl-*α*-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 σ-bond metathesis with the silylborane reagent were originally reported by Oestreich and subsequently developed by many researchers.[14] The electrophilic amination of organocopper species was also studied by some research groups.[10] 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 *α,β*-unsaturated carbonyl compounds were reported, but the tandem functionalization at the α position still remains a challenge, except for a few successful examples of the aldol-type reaction.[15] Therefore, suppression of the undesired protonation is the most important task for the development 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 *α,β*-Unsaturated Esters 1 with $PhMe_2Si$-Bpin and Hydroxylamines 2[a]



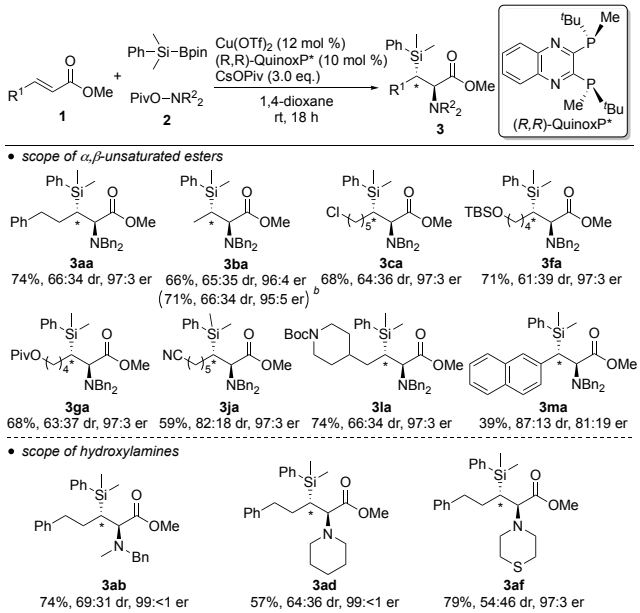
[a]Conditions: **1** (0.50 mmol), $PhMe_2Si$-Bpin (0.63 mmol), **2** (0.25 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.030 mmol), *p*-^{t}Bu-dppbz (0.030 mmol), CsOPiv (0.75 mmol), 1,4-dioxane (1.0 mL), rt, 18 h, N_2. Isolated yields are shown. [b]On 1.0 mmol scale. [c]With *O*-benzoylhydroxylamine.

Optimization studies commenced with methyl (*E*)-5-phenylpent-2-enoate (**1a**), $PhMe_2Si$-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 $Cu(OAc)_2 \cdot H_2O$/*p*-^{t}Bu-dppbz catalyst and a CsOPiv base to form the targeted *β*-silyl-*α*-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 *β*-silyl-*α*-amino acid derivatives **3ca**–**la** in moderate to good yields. Additionally, several cinnamates 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 *β*-silyl-*α*-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 *β*-silyl-*α*-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 $Cu(OTf)_2$/(*R,R*)- QuinoxP* catalysis[16] (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 *β*-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 *α*-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 *β*-silyl-*α*-amino acids **3ca**, **fa**, **ga**, **ja**, and **la** 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 *β*-silyl-*α*-amino acids **3ab**, **ad**, and **af** with high enantioselectivity.

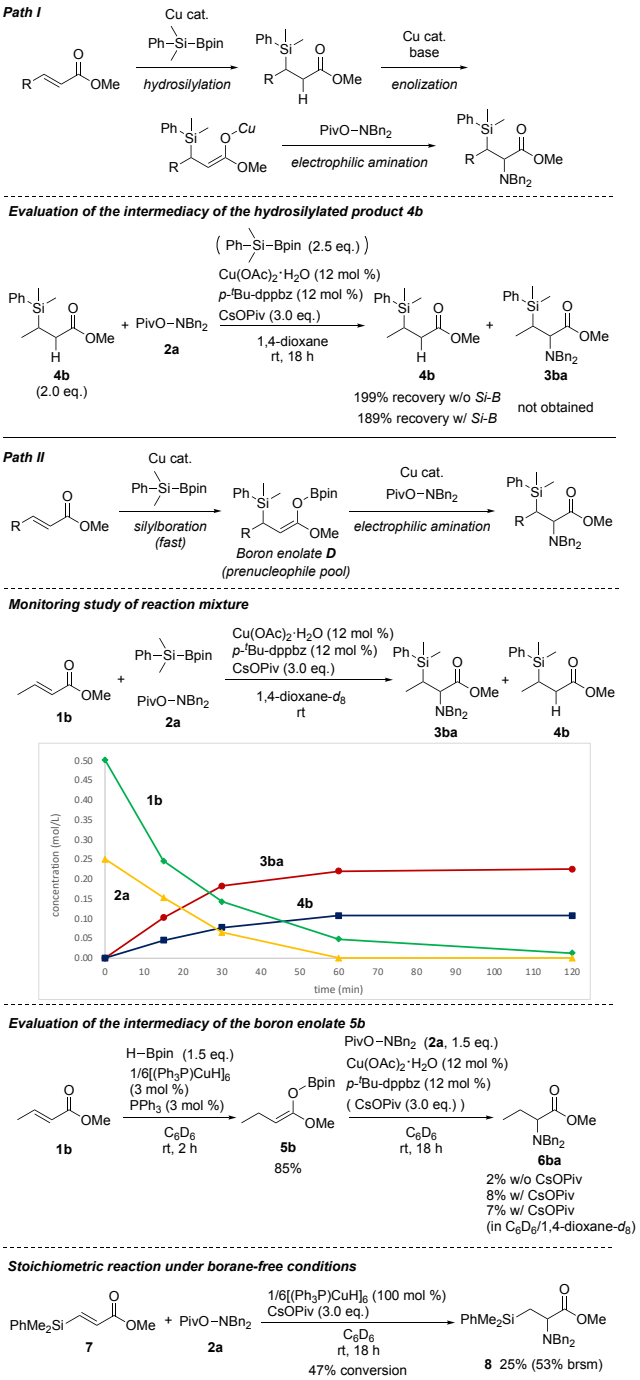
Scheme 3. Copper-Catalyzed Enantioselective Silylamination of *α,β*-Unsaturated Esters 1 with $PhMe_2Si$-Bpin and Hydroxylamines 2[a]



[a]Conditions: **1** (0.50 mmol), $PhMe_2Si$-Bpin (0.63 mmol), **2** (0.25 mmol), $Cu(OTf)_2$ (0.030 mmol), QuinoxP* (0.025 mmol), CsOPiv (0.75 mmol), 1,4-dioxane (1.0 mL), rt, 18 h, N_2. Isolated yields are shown. [b]On a 1.0 mmol scale.

We then performed some mechanistic studies. In Scheme 1d, the α,β-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 $PhMe_2Si$-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 prenucleophile pool, boron enolate **D**,[14e] then undergoes the copper-catalyzed electrophilic amination. To investigate this possibility, we monitored a reaction mixture of **1b**, $PhMe_2Si$-Bpin, and **2a** by ^1H NMR in 1,4-dioxane-d_8. 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 $PhMe_2Si$-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,[17] 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_6D_6/1,4-dioxane-d_8 mixed solvent system. These findings suggest

Scheme 4. Other Possible Pathways and Evaluation of Potential Intermediates



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 β-silyl-α-aminosilane **8** was formed from stoichiometric amounts of $[(Ph_3P)CuH]_6$, β-silyl-α,β-unsaturated ester **7**, and hydroxylamine **2a** even under the borane-free conditions.

In conclusion, we have developed a copper-catalyzed silylamination of *α,β*-unsaturated esters with silylboranes and *O*-pivaloylhydroxylamines to form the corresponding *β*-silyl-*α*-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 *β*-silyl-*α*-amino acids of high potential in medicinal chemistry. Further manipulation of products, improvement of diastereoselectivity,[18] 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.

^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}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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