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Copper-Catalyzed Stereo- and Enantio-selective 1, 4-Proto-silylation of α, β-Unsaturated Ketimines to Synthesize Functionalized Allylsilanes

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Supporting Information Placeholder

ABSTRACT: Copper-catalyzed conjugate proto-silylation reaction of *α, β*-unsaturated sulfonyl ketimines has been developed. The corresponding *E*- and *Z*-stereoselective functionalized allylsilane products were obtained in good yields respectively via tuning the ligands used in the reactions. Furthermore, the highly enantioselective (*E*)-*β*-tosylamine-substituted allylsilanes were also achieved in the presence of chiral Pybox ligand. And the corresponding products could be easily transformed into other useful synthons.

KEYWORDS: *conjugate proto-silylation, allylsilanes, copper-catalyst, regioselectivity, stereoselectivity*

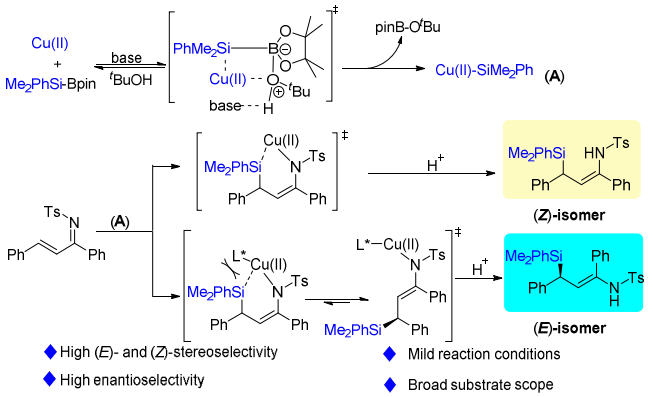
INTRODUCTION

Tremendous efforts have been devoted to discovering new methodologies for the synthesis of the allylic silanes because of their broad applications in organic synthesis and materials science.[1] Among them, transition-metals such as Ni,[2] Pd,[3] Pt[4] catalyzed silaborations of 1,3-dienes or allenes, and Cu-catalyzed allylic substitution[5] with use of Suginome silaboronate reagent[6] have emerged as very powerful tools for the preparation of these compounds. Nevertheless, to access the multi-substituted functionalized allylsilanes, the development of practical and efficient methods still remains highly desirable. Therefore, we design a copper-catalyzed conjugate proto-silylation of *α, β*-unsaturated ketimines to synthesize the stereo- and enantio-selective functionalized allylsilanes via trapping the double bond generated *in situ* during silyl-addition process (Scheme 1). It is worth noting that the transition-metal-catalyzed silyl-additions to conjugate carbonyl systems have attracted much attention. For instance, in 1988 Hayashi initially disclosed a 1,4-disilylation reaction with palladium catalyst.[3a, 7a] Alternatively, Oestreich,[7b] Hoveyda,[7c] Riant,[7d] Córdova,[7e] Santos,[7f] and Procter[7g] et al. elegantly developed different strategies using Rh(I)-binap, Cu(I)-NHC, Cu(I)-dppf, Cu(I)-amine or Cu(II)-4-picoline etc[8] system for the conjugate silyl-addition, respectively. Unfortunately, these methods are difficult to access the allylsilane product.

On the other hand, a few examples of conjugate addition to *α, β*-unsaturated imines to access nitrogen-containing moieties have also been studied. However, the works mainly focused on the construction of C-C bond by using organozinc reagents,[9] organocuprates,[10] organoboronic acids,[11] and other carbon-based nucleophiles in the presence of Rh, La,[12] or Cu catalyst. So far, only scarce examples of heteroatom-carbon bond formation via conjugate addition to *α, β*-unsaturated imines have been documented. Firstly, in 2009 Palacios et al. reported a non-enantioselective conjugate addition of amines to active *α, β*-unsaturated imines derived from α-amino phosphonates.[13a] After that, Leung and co-workers developed a Pd-catalyzed asymmetric addition of Ph_2PH to *α, β*-unsaturated sulfonyl ketimines and got the solo (*Z*)-configuration enaminophosphines.[13b] Recently, a copper-catalyzed conjugate borylation of ketimines was also addressed to prepare *β*-boronate-substituted imines.[13c] Unfortunately, so far there no study disclosed the stereo- and/or enantio-selective silyl-addition to *α, β*-unsaturated ketimines. In connection with our continuous interest in C-Si bond formation,[14] herein we would like to communicate the results of copper-catalyzed conjugate proto-silylation of *α, β*-unsaturated ketimines to access highly stereo- and enantio-selective *β*-tosylamine-substituted allylsilanes.

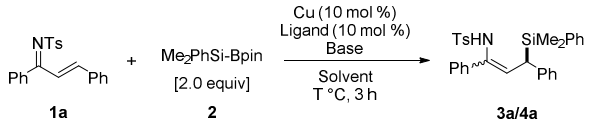
RESULTS AND DISCUSSION

Initially, the reaction of copper-catalyzed conjugate proto-silylation of *α, β*-unsaturated ketimine was examined with use of ketimine **1a** and Suginome silaboronate **2**, and the results were shown in Table 1. We first conducted the reaction with various Cu(I) and Cu(II) salts under basic condition (Table 1, entries 1-4). It was found that both of them could provide the desired product. Especially, in presence of 10 mol % $Cu(OTf)_2$ and 20 mol % Na_3PO_4 as the additive, the major product with a



Scheme 1. Copper-Catalyzed Stereo- and Enantio-selective 1, 4-Proto-silylation of *α, β*-Unsaturated Ketimine.

Table 1. Optimization of Reaction Conditions of Non-enantioselective Product.[a]



1a **2** **3a/4a**

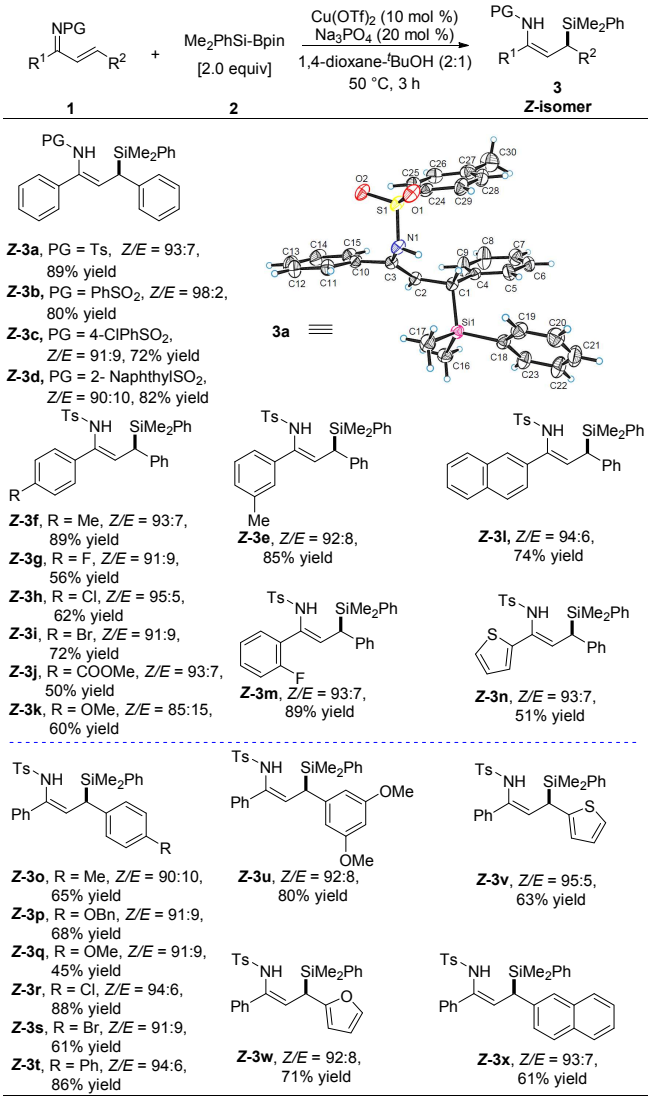
Entry	Cu (mol %)	Base (equiv)	Solvent (V/V=2/1)	T (℃)	*E*/*Z* (%)[b]	Yield (%)[c]
1	CuCl	Na_3PO_4 (0.2)	dioxane-^{t}BuOH	50	26:74	46
2	CuBr	Na_3PO_4 (0.2)	dioxane-^{t}BuOH	50	37:63	23
3	$Cu(OAc)_2$	Na_3PO_4 (0.2)	dioxane-^{t}BuOH	50	20:80	63
4	**$Cu(OTf)_2$**	**Na_3PO_4 (0.2)**	**dioxane-^{t}BuOH**	**50**	**7:93**	**91(89)**
5	$Cu(OTf)_2$	K_3PO_4 (0.2)	dioxane-^{t}BuOH	50	14:86	61
6	$Cu(OTf)_2$	-	dioxane-^{t}BuOH	50	-	trace
7	-	Na_3PO_4 (0.2)	dioxane-^{t}BuOH	50	-	trace
8	$Cu(OTf)_2$	Na_3PO_4 (0.2)	dioxane-^{t}BuOH	25	15:85	66
9	$Cu(OTf)_2$	DIPEA (0.2)	dioxane-^{t}BuOH	25	72:28	40
10	$Cu(OTf)_2$	DIPEA (3.0)	dioxane-^{t}BuOH	25	75:25	60
11	$Cu(OTf)_2$	DIPEA (3.0)	*m*-Xylene-^{t}BuOH	25	82:18	70
12[d]	$Cu(OTf)_2$	DIPEA (3.0)	*m*-Xylene-^{t}BuOH	-5	88:12	20
13[d, e]	$Cu(OTf)_2$	DIPEA (3.0)	*m*-Xylene-^{t}BuOH	-5	99:1	46
14[d, e, f]	CuTc	DIPEA (3.0)	*m*-Xylene-^{t}BuOH	-5	92:8	80
15[d, e]	$Cu(OAc)_2$	DIPEA (3.0)	*m*-Xylene-^{t}BuOH	-5	98:2	86(83)
16[d, e, g]	$Cu(CHB)_2$	DIPEA (3.0)	*m*-Xylene-^{t}BuOH	-5	98:2	92(90)
17[d, e, h]	**$Cu(CHB)_2$**	**DIPEA (3.0)**	***m*-Xylene-^{t}BuOH**	**-5**	**99:1**	**91(90)**

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), copper catalyst, and base in the solvent (1.50 mL in total volume) was heated for the indicated time. [b]The ratio between *E* and *Z* isomers was determined by crude ^{1}H-NMR analysis. [c]The yield given is for single *E* or *Z* isomer which was determined by ^{1}H-NMR (2, 4, 5-trichloropyrimidine as an internal standard). And the isolated yield is in the parentheses. [d]The reaction time is 36 h. [e]10 mol % 2, 2'-bipyridine was added as the ligand. [f]CuTc = ((thiophene-2-carbonyl)oxy)copper. [g]$Cu(CHB)_2$ = copper bis(4-cyclohexylbutyrate). [h]5 mol % $Cu(CHB)_2$ was used in the reaction.

(*Z*)-configuration (*Z*/*E* = 97:3) was obtained in 89% isolated yield (entry 4). Nonetheless, the change of base or reaction temperature noticeably decreased the reaction efficiency (Table 1, entries 5 and 8). It was also observed that the ratio of (*E*)-isomer greatly increased in the presence of organic base *N*, *N*'-diisopropylethylamine (DIPEA). Thus, we hypothesized that increasing the steric hindrance around the copper center could regulate the product's stereoselectivity. Therefore, the 2,2⍰-bipyridine with strong coordinated-ability was introduced to this catalytic system (Table 1, entry 13). It is worth noting that the desired product can be obtained in a moderate yield but with an excellent (*Z*)-stereoselectivity. After further carefully screening the copper salts, pleasingly, the (*E*)-isomer of *β*-tosylamine-substituted allylsilane could be isolated in high yield and with excellent stereoselectivity by using $Cu(CHB)_2$ (copper bis (4-cyclohexylbutyrate)) as a catalyst. Notably, the copper catalyst and base used in reaction were both crucial to afford the desired product (Table 1, entries 6 and 7).

With the optimal conditions determined, the substrate scope of *α, β*-unsaturated ketimine was explored for (*Z*)- and (*E*)-stereoselective synthesis of *β*-tosylamine-substituted allylsilanes, respectively. The results are presented in Tables 2 and 3. In both cases, different *N*-arylsulfonyl ketimines reacted with dimethylphenylsilylpinacolborane (Me_2PhSi-Bpin) **2**. The results showed that the tosylsulfonyl group more favored the formation of specifically stereoselective product in a good yield. Next, the substituent effect of R^1 and R^2 was also investigated. As indicated in Tables 2 and 3, varying the position of R^1 and R^2 substituents on the phenyl ring, regardless of the electron-donating or electron-withdrawing group, the corresponding products could be obtained in good to high yields and with a high to excellent level of stereoselective control. Moreover, both these processes tolerated a wide range of functionalized groups, such as ester, halogens (F, Cl, Br) and heterocycles (thienyl, furyl). The relative stereo configuration of (*Z*)-isomer product **3a** was confirmed by X-ray single crystal diffraction analysis (CCDC No: 1837165).

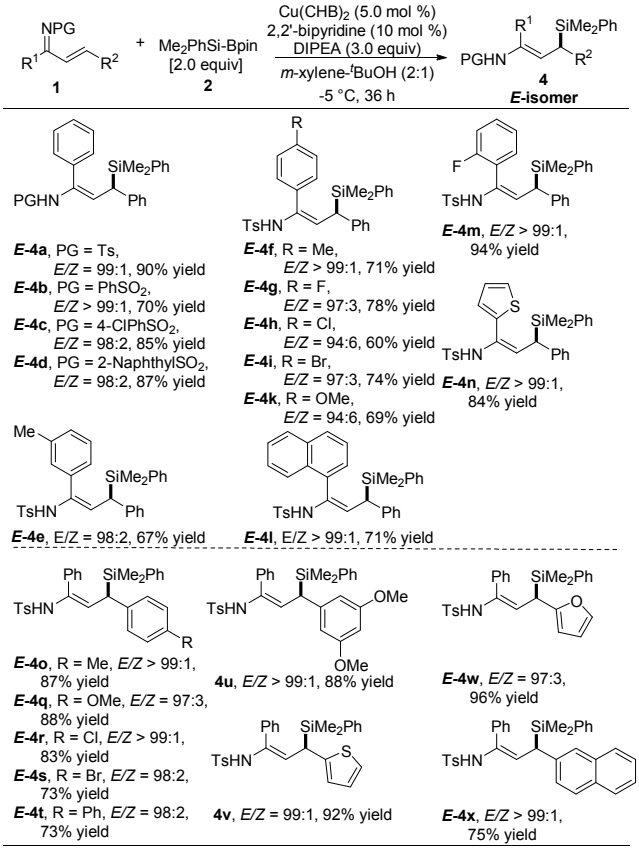
Table 2. Non-enantioselective Conjugate Proto-silylation of *α, β*-Unsaturated Ketimines for the Synthesis of (*Z*)-isomer Allylsilane.[a, b]



[a]Reaction conditions: the mixture of **1** (0.2 mmol), **2** (0.4 mmol), $Cu(OTf)_2$ (0.02 mmol), Na_3PO_4 (0.04 mmol) in 1,4-dioxane/^{t}BuOH (2:1, 1.5 mL) solution was stirred for 3 h at 50°C under argon atmosphere. [b]The isolated yield is for *Z*-isomer only.

Base on the investigation for the synthesis non-enantioselective *E*-isomer allylsilane products, we embarked on developing the methodology of asymmetric conjugate proto-silylation to *α, β*-unsaturated ketimines. According to the previous reports on Cu(II)-catalyzed asymmetric addition reactions, we first tested various chiral ligands such as chiral phosphoric acid,[15] phosphine,[16] NHC,[17] phosphoramide[18] and oxazoline[19] etc. for current asymmetric silyl addition reaction. Unfortunately, only very poor enantioselectivity of the desired product was observed. When the commercially available Pybox-^{i}Pr (**L$_1$**) was used to this catalytic system, the compound **4a** was obtained in a high yield and with a moderate enantiomeric ratio (89:11). Therefore, to obtain a high-level enantioselectivity, various substituted Pybox ligands were subjected to this addition reaction (Table 4). Consequently, after a careful screening, we realized that the Pybox ligand with an alkyl-substituent would afford a better result than the one bearing

Table 3. Non-enantioselective Conjugate Proto-silylation of *α, β*-Unsaturated Ketimines for the Synthesis of (*E*)-Isomer Allylsilane.[a]

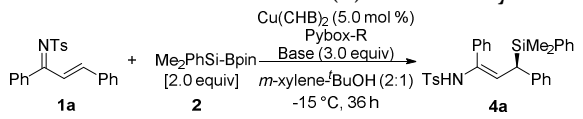


[a]Reaction conditions: The mixture of **1** (0.2 mmol), **2** (0.4 mmol), $Cu(CHB)_2$ (0.01 mmol), 2, 2'-bipyridine (0.02 mmol), and DIPEA (0.6 mmol) in *m*-xylene/ ^{t}BuOH (2:1, 1.5 mL) was stirred for 36 h at -5 °C under argon atmosphere. [b]The isolated yield is for *E*- isomer only.

with an aryl substituent. However, bulkier alkyl-substituted Pybox ligands especially the one with the *tert*-butyl substituent will significantly decrease the product's enantioselectivity. This was possibly due to the weak interaction between the ligand and the copper atom center caused by the large steric hindrance. Thus, the less bulky *iso*-butyl-substituted Pybox was prepared and examined for this reaction. Pleasingly, the desired product was isolated in 90% yield and with 91.5:8.5 enantiomeric ratio. Furthermore, we recognized that if connecting a phenyl substituent on the pyridyl ring[20] to result a *π-π* interaction between the ligand and dimethylphenylsilyl group should increase the product's enantioselectivity. Thus, we synthesized the chiral (*S, S*)-4-Ph-Pybox-^{s}Bu as a ligand for this reaction and observed a slightly increased enantioselectivity of the product. It is worth noting that our hypothesis has also been proved by the poor results by changing the (*S, S*)-4-Ph-Pybox-^{s}Bu ligand into (*S, S*)-4-*tert*-butyl-Ph-Pybox-^{s}Bu or (*S, S*)-4-Mes-Pybox-^{s}Bu, which will diminish the *π-π* interaction between the phenyl rings due to their increased space resistance. Finally, we found that the desired allylsilane **4a** could be obtained in 90% yield and with 95:5 enantiomeric ratio in presence of 5 mol % copper bis (4-cyclohexylbutyrate), 20 mol % (*S, S*)-4-Ph-Pybox-^{s}Bu, and

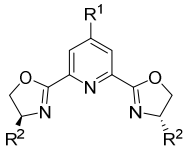
2,6-di-*tert*-butylpyridine (3.0 equiv) in the mixed solvents of *m*-xylene and *tert*-butanol (V: V = 2:1) at -15 ℃ (entry 10).

Table 4. Optimization of Reaction Conditions for the Synthesis of Enantioenriched (*E*)-Isomer Allylsilane.[a]



1a 2 4a

Entry	Ligand (mol %)	Base	*E* / *Z* (%)[b]	Yield (%)[c]	er (%)[d]
1	L_1 (10)	DIPEA	97:3	94	89:11
2	L_2 (10)	DIPEA	80:20	63	56.5:43.5
3	L_3 (10)	DIPEA	94:6	92	80:20
4	L_4 (10)	DIPEA	> 99:1	98	60:40
5	L_5 (10)	DIPEA	80:20	63	55.5:44.5
6	L_6 (10)	DIPEA	98:2	90	91.5:8.5
7	L_7 (10)	DIPEA	95:5	88	93.5:6.5
8	L_7 (10)	2,6-di-*tert*-butylpyridine	97:3	93(90)	94:6
9	L_7 (15)	2,6-di-*tert*-butylpyridine	95:5	90	94:6
10	**L_7 (20)**	**2,6-di-*tert*-butylpyridine**	**95:5**	**91 (90)**	**95:5**
11[e]	L_7 (20)	2,6-di-*tert*-butylpyridine	98:2	85	93.5:6.5
12	L_8 (20)	2,6-di-*tert*-butylpyridine	96:4	91	90:10
13	L_9 (20)	2,6-di-*tert*-butylpyridine	96:4	91	93:7



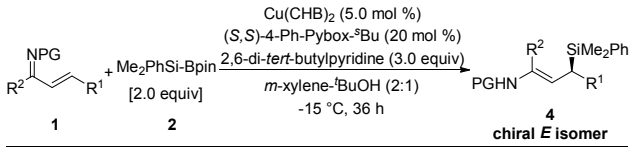
L_1: R^1 = H, R^2 = ^{i}Pr
L_2: R^1 = H, R^2 = ^{t}Bu
L_3: R^1 = H, R^2 = Cy
L_4: R^1 = H, R^2 = Ph
L_5: R^1 = H, R^2 = Bn
L_6: R^1 = H, R^2 = ^{s}Bu
L_7: R^1 = Ph, R^2 = ^{s}Bu
L_8: R^1 = 4-^{t}Bu-Ph, R^2 = ^{s}Bu
L_9: R^1 = Mes, R^2 = ^{s}Bu

[a]Unless noted otherwise, the reaction was conducted according to following conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Cu(CHB)_2$ (0.01 mmol), ligand (0.04 mmol), and base (0.6 mmol) in *m*-Xylene/^{t}BuOH (2:1, 1.5 mL) were stirred for 36 h at -15 °C under argon atmosphere. And the isolated yield is for *E*- isomer. [b]The ratio of the isomers was determined by crude ^{1}H-NMR analysis. [c]The yield was determined by ^{1}H-NMR (2, 4, 5-trichloropyrimidine as an internal standard). And the isolated yield was given in the parentheses. [d]The enantiomeric ratios were determined by HPLC with the chiral column. [e]$Cu(OAc)_2$ was used in place of $Cu(CHB)_2$.

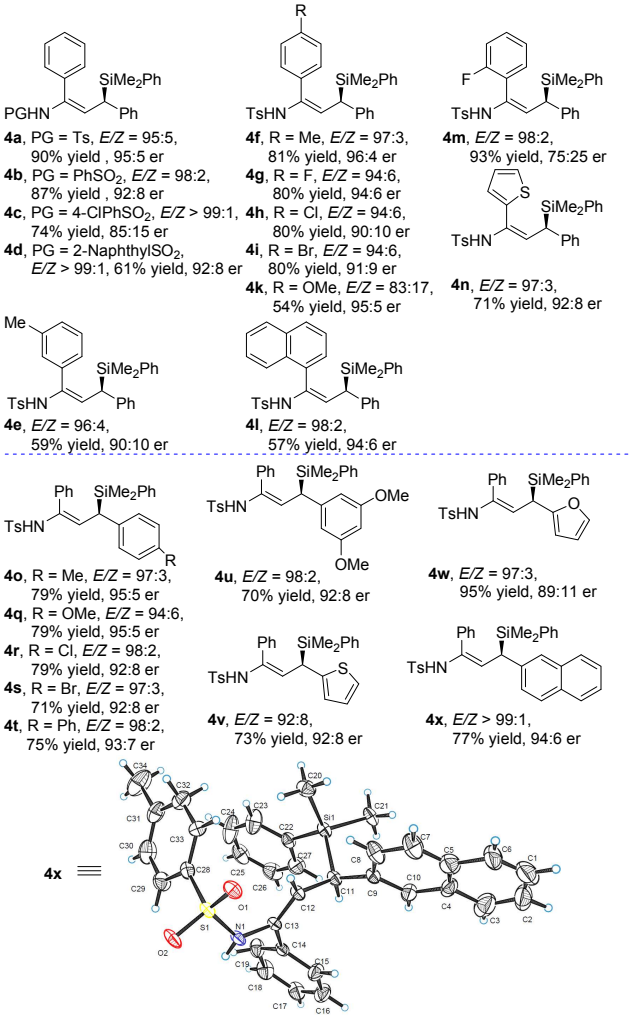
On account of the optimal conditions, the practicability of the Cu(II)/(*S*, *S*)-4-Ph-Pybox-^{s}Bu species catalyzed asymmetric conjugate proto-silylation of various *α*, *β*-unsaturated ketimines was confirmed (Table 5). The reaction could be conducted with different ketimines with a tolerance of both electron-donating and-withdrawing substituents. And the desired *E*-stereoisomers with high enantiomeric ratios were obtained in good to high yields. In most of cases, better enantioselectivity and lower reactivity were observed for the electron-rich substrates, which could be explained by the lower electrophilicity and stronger interaction between the ketimine and the [Me_2PhSi-Cu(II)]/Pybox species generated in *situ*. The compound **4x** was determined to be (*R*)-configuration by single-crystal X-ray diffraction analysis (CCDC No: 1837166).

Taking into account the previous reports on activation of Si-B bond and the formation of [Me_2PhSi-Cu(II)] reactive intermediate,[7e] we proposed a stereochemical model for generating the enantioenriched *β*-tosylamine-substituted allylsilane (Figure 1). Comparing, in transition state **A** with **B**, the minimum steric interaction between the isobutyl group of the ligand and the tosyl group of the substrate as well as the *π*-*π* stacking interaction of phenyl rings, both favor the nucleophilic [Me_2PhSi-Cu(II)] intermediate to attack the double bond from the *Re*-face and afford the (*R*)-isomer preferentially.

Table 5. Asymmetric Conjugate Proto-silylation of *α*, *β*-Unsaturated Ketimines.[a, b]



1 2



[a]Reaction conditions: The mixture of **1** (0.2 mmol), **2** (0.4 mmol), $Cu(CHB)_2$ (0.01 mmol), (*S, S*)-4-Ph-Pybox-^{s}Bu (0.04 mmol), and 2,6-di-*tert*-butylpyrdine (0.6 mmol) in

m-xylene/^{t}BuOH (2:1, 1.5 mL) at -15 °C was stirred for 36 h under argon atmosphere. [b]The isolated yield is for *E*-isomer only.

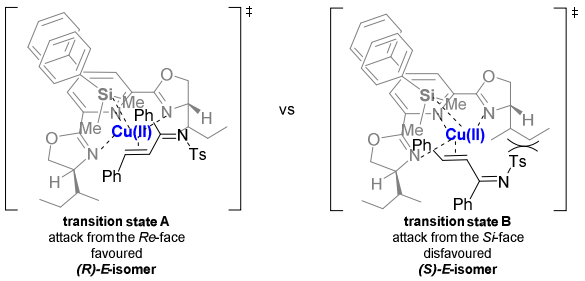
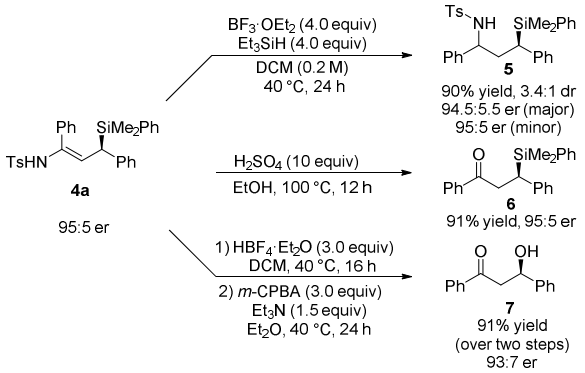


Figure 1. Proposed Model for Formation of (*R*)-4a Compound.



Scheme 2. Transformation of *β*-Tosylamine-Substituted Allylsilanes.

Finally, the utility of *β*-tosylamine-substituted allylsilane products was demonstrated in Scheme 2. Notably, the gram-scaled synthesis of compound **4a** was performed in 89% isolated yield (2.21 g) and without loss of the enantioselectivity (95:5 er) in the presence of 5 mol % $Cu(CHB)_2$ catalyst. The reduction of **4a** with use of $Et_3SiH/BF_3{\bullet}OEt_2$ was carried out to provide the *β*-tosylamine-substituted benzylic silane in good yield (90%) and moderate diastereoselectivity (3.4:1 dr).[21] In addition, the hydrolysis product **6** was obtained in high yield and with complete retention of enantiopurity when the compound **4a** was treated with sulfuric acid in ethanol.[11b] The Fleming-Tamao oxidation[22] of the compound **4a** successfully afforded the chiral 3-hydroxy-1,3-diphenylpropan-1-one **7** in 91% yield and 93:7 er over two steps.

CONCLUSION

In conclusion, we have developed a protocol of copper-catalyzed stereo- and enantio-selective conjugate silyl-addition to sulfonyl ketimines. This work offers a simple and straightforward method for the synthesis of not only the (*Z*)-*β*-tosylamine-substituted allylsilane but also the *E*-isomer in good yields and with high enantioselectivities via simply tuning the reaction temperature and the ligand used. Moreover, the corresponding products are effective synthons for the preparation of useful compounds.

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Notes
The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI:.
Supporting spectra and characterization data (PDF)
Crystallographic data for compound **3a** and **4x** (CIF)

ACKNOWLEDGMENT

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