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NHC-Copper-Catalyzed Asymmetric Conjugate Silylation of Access Chiral α-Aminosilanes

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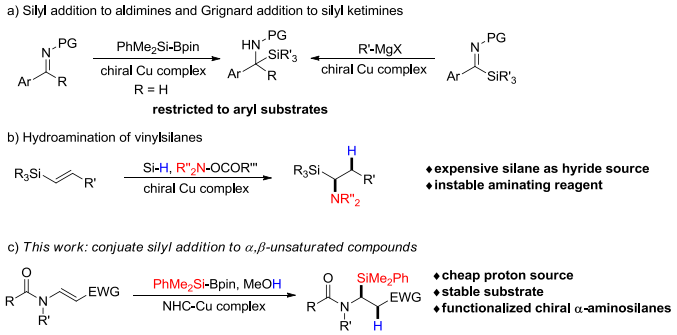
ABSTRACT

Chiral α-aminosilane and its derivatives have found potential applications in pharmaceuticals. Yet there are rare examples have been reported for the synthesis of these molecules. Herein we report a catalytic asymmetric conjugate silylation reactions of β-amido-acrylonitriles and β-amido-acrylates for the first time in the presence of catalytic amount of chiral N-heterocyclic carbene (NHC)/Copper(I) complex. A variety of functionalized chiral α-aminosilanes were obtained at room temperature in good yields with high enantioselectivities in the presence of NHC (10 mol%), CuCl (10 mol%), NaOtBu or NaOMe (20 mol%), and MeOH (2 equivalents).

Introduction

Optically active Organosilane compounds have found widespread applications in both synthetic and medicinal chemistry.[1,2] Among these, chiral α-aminosilanes have gained increasing attention because they have shown significant bioactivities and served as the key constituents of peptidomimetics.[2,3] Accordingly, many methods have been developed in the synthesis of these structures.[4,5] However, only a few examples have been reported for their asymmetric synthesis. The traditional diastereoselective synthesis requires organolithium reagents, which usually suffers from limitations such as narrow functional group tolerance and harsh reaction conditions. In this context, examples include reverse aza-Brook rearrangement[6-8] and the addition of silyllithium reagents to the chiral aldimines.[3,9-13] On the other hand, copper-catalyzed asymmetric transformations provide mild and straightforward approaches to access these structures with wide functional group compatibility. Examples in this aspect include silyl addition to the aldimines,[14] addition of Grignard reagents to the aromatic silyl ketimines,[15] hydroamination and aminoboration of vinyl silanes.[16] However, there are still some limitations. For examples, reactions of aldimines or silyl ketimines are restricted to aryl substrates; hydroamination of vinylsilanes requires expensive silanes as hydride source and instable aminating reagents. In addition, catalytic methods to synthesizing chiral α-aminosilanes with functional groups such as ester, cyanide, amide, and halogens remain virtually unexplored,[6-8] which hamper further applications of these methods. Thus, it is still appealing to develop efficient methods to prepare α-aminosilanes with multiple functionalities.



Scheme 1. Strategies to synthesis of Chiral α-aminosilanes via asymmetric catalysis.

Transition-metal-catalyzed β-silylation of α,β-unsaturated compounds have received considerable attention in synthesizing optically active chiral α-silanes.[17-22] In particular, inexpensive copper complexes are able to efficiently give silyl transfer to cyclic and acyclic α,β-unsaturated carbonyl compounds with high enantioinduction.[20-22] However, none of them have been used to β-heteroatom substituted substrates. The deficiency of research is probably caused by deactivation of substrates through

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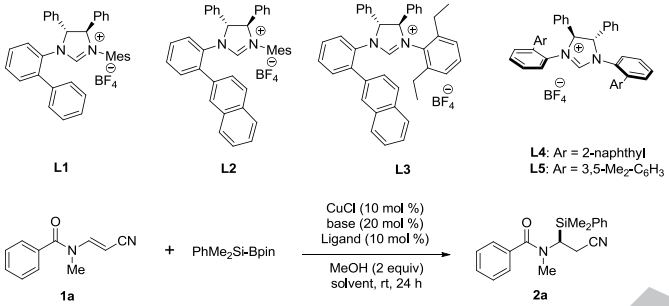
the interaction of a lone pair of electrons of the heteroatom with the conjugated π-system of the olefin moiety.[23] Moreover, the heteroatoms are usually good leaving groups, which would cause the elimination of heteroatoms.[24] Despite these problematic issues, the reaction of α,β-unsaturated compounds containing a β-nitrogen substituent with silyl reagent may provide an alternative approach to provide chiral α-aminosilanes. We envisioned that the deactivation and deamination could be minimized by judicious choice of substituents on nitrogen. Herein, we report a copper-catalyzed asymmetric β-silylation of β-amidoacrylonitriles and β-amidoacylate esters under mild reaction conditions, providing functionalized chiral α-aminosilanes in good to excellent enantioselectivities.

Results and Discussion

Table 1 Optimization of Copper-Catalyzed Asymmetric Conjugate Silylation of β-Amido-acryonitrile **1a**.

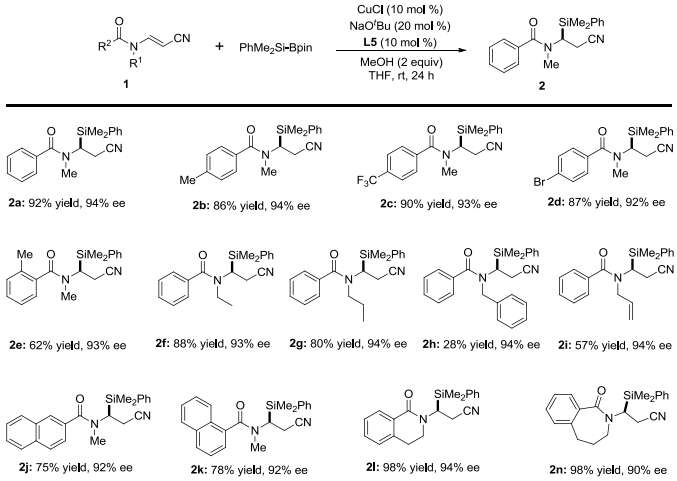


Entry	L	Base	Solvent	yield/%[a]	ee/%[b]
1	**L1**	NaO*t*-Bu	THF	94	75
2	**L2**	NaO*t*-Bu	THF	94	79
3	**L3**	NaO*t*-Bu	THF	95	81
4	**L4**	NaO*t*-Bu	THF	64	88
5	**L5**	NaO*t*-Bu	THF	92	94
6	**L5**	KO*t*-Bu	THF	87	94
7	**L5**	LiO*t*-Bu	THF	36	90
8	**L5**	NaO*t*-Bu	Toluene	88	94
9	**L5**	NaO*t*-Bu	CH_2Cl_2	Trace	81
10	**L5**	NaO*t*-Bu	CH_3CN	94	83
11	**L5**	NaO*t*-Bu	*n*-Hexane	91	92

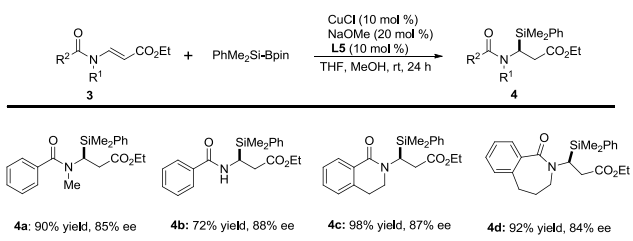
[a] Isolated yields. [b] Determined by Chiral HPLC.

Recently, we reported a copper-catalyzed borylation of β-amido-acrylonitriles and β-amido-acrylates using chiral phosphines as ligands.[24] However, when we applied this protocol to the silylation, only a trace amount of product was observed. The reason is probably due to less nucleophilicity of silylcopper species than its boryl analog. Therefore, a ligand with the strong σ donating ability (such as N-heterocyclic carbene (NHC)) is a necessity to force this reaction to happen. Gratifyingly, the reaction of β-amido-acrylonitrile **1a** with $PhMe_2Si$-Bpin (2.0 equivalents) in the presence of MeOH (2 equivalents), 10 mol% CuCl, 10 mol% C_1-symmetric imidazolinium **L1** and 20 mol% NaO*t*-Bu in THF at room temperature underwent smoothly, affording corresponding silylated product **2a** in 94% yield with 75% ee within 24 h (Table 1, entry 1). The reaction did not complete when reducing the amount of $PhMe_2Si$-Bpin. Notably, no product was observed without MeOH, **L1** or NaO*t*-Bu. We then focused on the effects of *N*-aryl substituents on chiral induction. Replacement of a phenyl group of **L1** with 2-naphthyl group (**L2**) slightly enhanced enantioselectivity (Table 1, entry 2, 79% ee). The use of a more sterically congested 2,6-2,6-diethylphenyl group substituted ligand **L3** could improve enantioselectivity further (Table 1, entry 3, 81%). To further enhance the enantioselectivity of the current reaction, we turned our attention from C_1-symmetric ligands **L1**-**L3** to C_2-symmetric ones **L4** and **L5**. Pleasingly, 88% ee was obtained albeit with moderate isolated yield in the presence of ligand **L4** bearing two 2-naphthyl groups . 3,5-Dimethylphenyl substituted ligand **L5**provided **2a** in 92% yield and 94% ee. With optimized ligand **L5** in hand, we then investigated other reaction conditions such as solvent and base as shown in Table 1 (entries 6-11). The results showed that reaction conditions in entry 5 were optimal.

With optimized reaction conditions in hand, we then turned our attention to the substrate scope of the current reaction (Scheme 2). Substituents of benzoate groups have negligible effects on enantioselectivities, giving products with uniformly excellent enanatioselectivities (**2a-e**, 92-94% ee). And most of them were obtained in high yields (**2a-d**, 86-92%). *Ortho*-methyl benzoate substituted substrate gave the silylated product (**2e**) in moderate yield (62%) probably due to steric encumbrance. Next, we examined alkyl substituents on the nitrogen. Again, all of them provided consistently excellent enantioselectivities (**2f-i**, 93-94% ee). The low yield of **2h** (28%) probably arose from relatively bulky benzyl group. Interestingly, the reaction is compatible with the alkenyl group (**1i**) which is usually sensitive to silyl copper species. The untouched olefin motif of **2i** allows it to undergo further functionalization. Switching benzoyl to naphthoyl could also result in products **2j** and **2k** in good yields (75% and 78%, respectively) and excellent enantioselectivities (92% ees). The reaction could also applicable to substrates bearing lactams at β-position, giving products **2l** and **2m** in superior yields (both 98%) with excellent levels of stereoselectivities (94% and 92%, respectively).



Scheme 2. Copper-Catalyzed Asymmetric Conjugate Silylation of β-Amido-acryonitriles **1**.



Scheme 3. Copper-Catalyzed Asymmetric Conjugate Silylation of β-Amido-acrylates **3.**

To further demonstrate the generality of the current protocol, we next examined the reaction of ethyl β-aminoacylates **3** (Scheme 3). Gratifyingly, the use of same ligand **L5** could also provide efficient silyl transfer with good enantioinduction when NaOMe was used as the base instead of NaO*t*Bu. *N*-alkyl substituted substrates provided products in high yields (**4a**, **4c**, and **4d**, 90-98%) with good ee values (84-87%). Interestingly, the substrate **3b** bearing a free N-H group could also be compatible with the reaction conditions, giving **4b** in 72% yield with good enantioselectivity (88%). The free N-H group allows it to undergo further diversifications.

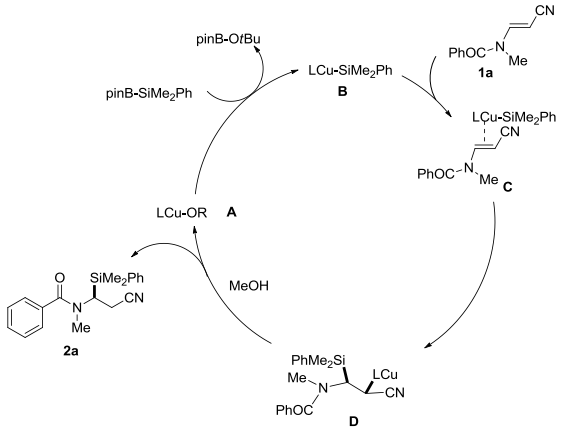


Figure 1. Plausible reaction mechanism.

Giving the importance of MeOH in promoting the reaction, we believed the reaction has a similar mechanism with other copper-catalyzed β-silylation of α,β-unsaturated compounds. Thus, a plausible mechanism is elucidated as shown in Figure 1. The reaction of in-situ generated copper alkoxide NHC-CuOR **A** with borylsilane via σ-bond metathesis gives silylcopper intermediate **B**.[25] Coordination of **B** with the carbon-carbon π-bond of **1a** followed by 3,4-addition would provide the complex **D** bearing a C-Cu bond.[26] Subsequent protonation of C-Cu bond results in the silylated product with the concurrent regeneration of species **A**.

Conclusion

In summary, we have developed an NHC-copper-catalyzed enantioselective β-silylation of β-amido acrylonitriles and β-amidoacrylates under mild reaction conditions for the first time. The reaction provides corresponding chiral α-aminosilanes in good yields with good to excellent enantioselectivities (84-94% ees). Application of silylated products and development of other asymmetric silylation reactions are currently underway in our laboratory.

Acknowledgments

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Supplementary Material

Supplementary material including experimental procedures and characterization data to this article can be found online.

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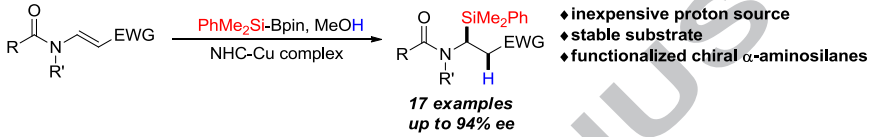

Highlights

- In situ formed inexpensive copper(I) complexes were used as catalysts.
- The reaction proceeded with high enantioselectivities under mild conditions.
- A series of potentially useful functionalized chiral α-aminosilanes were prepared.