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SHORT COMMUNICATION

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Stereoselective Synthesis of Highly Substituted α-Silylamines from Silylmethyl Azides under Ru Catalysis

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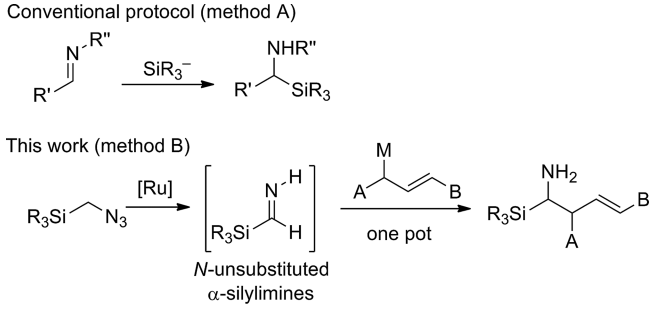
Keywords: Silicon / Azides / Ruthenium / Synthetic methods / Amines

A synthetic strategy towards highly substituted α-silyl homoallylic amines was discovered. The key event is the unique synthesis of *N*-unsubstituted α-silylimines from azide precursors under mild conditions. Of particular note is the unprecedented access to α-silylamines possessing multiple stereocenters and functional groups with high diastereo- and enantioselectivity. The synthetic utility of the method was demonstrated by the use of the silyl moiety as the key element that enables late-stage modification for the iminium ion mediated oxidative cyclization.

Introduction

Highly substituted α-silylamines are particularly attractive synthetic targets because of their unique structures and biological roles such as amino acid mimics.[1] Moreover, silyl groups are used as a versatile precursor that can be converted into various reactive intermediates with diverse chemical properties (Scheme 1). For example, α-silylamines can be turned into iminium ions in the presence of oxidants such as ceric ammonium nitrate.[2] Also, they can be transformed into aminyl radicals upon UV irradiation[3] or by the reaction with metal catalysts under photocatalytic conditions.[4] Moreover, the reaction of α-silylamines with electrophiles such as CO_2 can be initiated by fluoride ion activators.[5] Furthermore, α-silylamines are known to be stable under neutral conditions and can be easily carried through multistep synthetic sequences.

We have been interested in developing a conceptually new and divergent strategy based on organometal catalysis with the aim to synthesize three-dimensionally rich heterocyclic compounds with optimal chemical efficiency. On the basis of the cameleon-like reactivity discussed above,[6] we envisioned that the α-silyl moiety would enable a late-stage modification strategy that would generate structurally diverse amine scaffolds. On the basis of the importance of amine compounds in organic synthesis and the area of pharmaceuticals, this strategy should find significant use in both target-oriented and diversity-oriented syntheses.[7] Despite the potential significance, this new divergent strategy has not been discussed in organic synthesis, mainly because highly substituted and stereochemically diverse α-silylamines are not easily available. Generally, α-silylamines are prepared by the addition of silyl anions or derivatives to the imine compounds (Scheme 1, method A).[8,9] The scope of this reaction is largely limited to imines possessing no enolizable hydrogen atoms. In addition, the preparation of the silyl anions requires harsh conditions and/or multistep sequences. We reasoned that an alternative strategy involving the addition of alkyl anions to the *N*-unsubstituted α-silylimine species may be better suited for the proposed strategy. For example, addition of allylic nucleophiles to α-silylimines will install multiple functional groups and stereocenters that are necessary for further transformations in a diastereoselective and even in an enantioselective manner (Scheme 1, method B). However, little is known about the preparation of α-silylamines by way of this method. This is presumably due to problems associated with the preparation of the *N*-unsubstituted α-silylimines from their carbonyl precursors.[10,11] Recently, we developed the ruthenium-catalyzed synthesis of *N*-unsubstituted imines from alkyl azides under photolytic conditions.[12] Moreover, we demonstrated that homoallylic and homopropargylic amines could be directly accessed from alkyl



Scheme 1. Basic scheme for the synthesis of α-silylamines.

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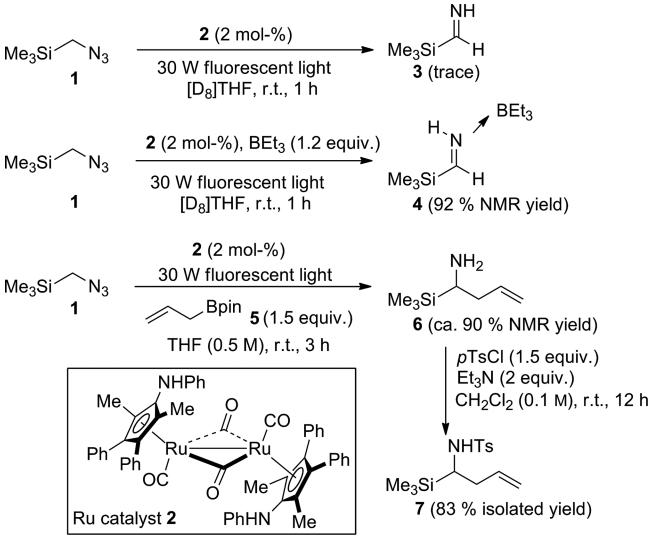
azides in a one-pot manner without the need for protecting groups by combining this imine generation with the reaction of allylic (and allenylic) boronate species. At the outset of the study, we envisioned that this protocol could be applicable to the synthesis of elusive α-silylamines.

Results and Discussion

To test the feasibility of the proposed synthetic method, we first investigated whether α-silylimine **3** could be generated from commercially available azide **1**[13a] under photolytic conditions. Upon treatment of **1** with diruthenium catalyst **2** (2 mol-%) under illumination with a 30 W fluorescent light in [D_8]THF, imine **3** was not observed, even though azide **1** was completely consumed (Scheme 2). In light of this disappointing result, we reasoned that unstable imine **3** might decompose under the reaction conditions. Notably, the addition of triethylborane (1.2 equiv.) led to the generation of imine–borane complex **4** in a significant 92% yield (determined by NMR spectroscopy). Because it appears that imine intermediate **3** is stabilized by the borane species, we turned our attention to the one-pot synthesis of α-trimethylsilyl homoallylic amine **6** by directly combining the Ru-catalyzed imine synthesis with the subsequent reaction with allylic boronate **5**. To our delight, α-silylamine **6** was generated in 90% yield (determined by NMR spectroscopy) in the presence of Ru catalyst **2** (2 mol-%) upon illumination with a 30 W fluorescent light (Scheme 2). However, our attempts to isolate **6** were unsuccessful because of its high volatility. As a consequence, compound **6** was protected with a *p*-toluenesulfonyl (Ts) group to generate compound **7**, which was isolated in 83% yield (over two steps). Notably, this reaction can be conducted on a multigram scale with no significant decrease in the yield.

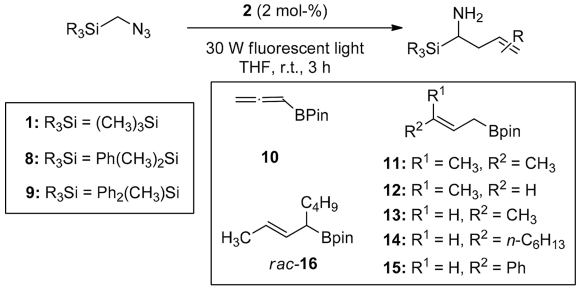


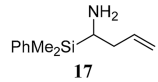
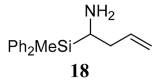
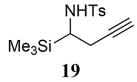
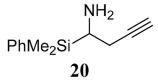
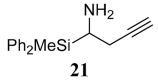
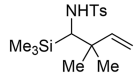
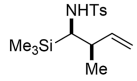
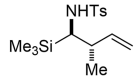
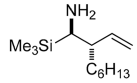
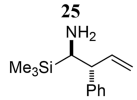
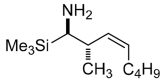
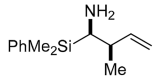
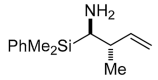
Scheme 2. Preliminary studies; pin = pinacolyl.

Having established the conditions for the one-pot protocol, we then investigated the scope of the reaction. First, we varied the alkyl substituents on the silicon moiety. Sterically bulky phenyldimethylsilyl and diphenylmethylsilyl groups were tolerated to give amines **17** and **18** in yields of 81 and 69%, respectively (Table 1, Entries 1 and 2). In addition, the use of allenyl boronates **10** also produced corresponding homopropargylated amine products **19**–**21** in good yields possessing various substitution patterns on the silicon atom (Table 1, Entries 3–5). As is the case for simple alkyl azides, synthesis of homopropargylic amines required a high temperature and a large amount of allenylboronate **10**.[12b] Upon using azide **1**, the amine product was isolated as *p*-toluenesulfonyl-protected **19** (Table 1, Entry 3). The reaction of 3,3-dimethylallylboronate gave **22** possessing a quaternary carbon center in good yield, even though the reaction required harsh conditions presumably as a result of steric hindrance between the alkyl substituents and the trimethylsilyl group (Table 1, Entry 6). Next, we investigated allyl boronates possessing various substituents at the terminal position to examine the diastereoselective synthesis of the α-silylamines. The reaction of azide **1** with (*Z*)-crotylboronate **12** showed excellent reagent-controlled diastereoselectivity; *syn* product **23** was generated in 83% yield with high selectivity (Table 1, Entry 7).[14] Using (*E*)-crotylboronate **13** provided diastereomeric *anti* product **24** in a comparable 82% yield, again with high diastereoselectivity (Table 1, Entry 8).[14] Conservation of the olefin geometry strongly suggests formation of a six-membered cyclic intermediate. The reaction of allylboronate possessing a longer aliphatic alkyl chain (Table 1, Entry 9) or a phenyl group with azide **1** (Table 1, Entry 10) had no detrimental effect on the yield and the selectivity; products **25** and **26** were delivered in high yields with high selectivities. Remarkably, the use of densely substituted racemic allylicboronate **16** gave **27** in 71% yield with approximately 90:10 selectivity (Table 1, Entry 11; for the determination of the structure of **27**, see below and the Supporting Information). Analysis of the coupling constant (J = 10 Hz) strongly suggested the exclusive formation of the (*Z*) olefin.[15] The reaction of isomeric crotylboronates **12** and **13** with azide **8** possessing a bulkier silyl group showed no significant negative effect on the reaction (Table 1, Entries 12 and 13).

Next, we investigated the reagent-controlled enantioselective synthesis of highly substituted α-silylamines. First, we performed the one-pot imine generation and the asymmetric allylation by using chiral allylborane. As shown in Scheme 3, generation of the *N*-unsubstituted imine at room temperature and subsequent asymmetric allylation with (–)-*B*-allyldiisopinocampheylborane [(–)-Ipc_2B(allyl)] at –78 °C gave the corresponding amine, which was then converted into *tert*-butoxycarbonyl (Boc) derivative **30** in 60% yield (over two steps) with 87% *ee*. The absolute configuration of the silylamine was assigned to be (*R*)[16] (for determination of the absolute configuration and the *ee*, see the Supporting Information). In addition, the use of sterically bulky azide **8** also gave amine (*R*)-**17** in 62% yield with 80% *ee*.[17] Another remarkable example in the enantioselective synthesis of α-silylamines is presented by the synthesis of (*R*)-**27**. Combining the use of enantioenriched allylic boronate **16**[18] with imine generation gave highly function-

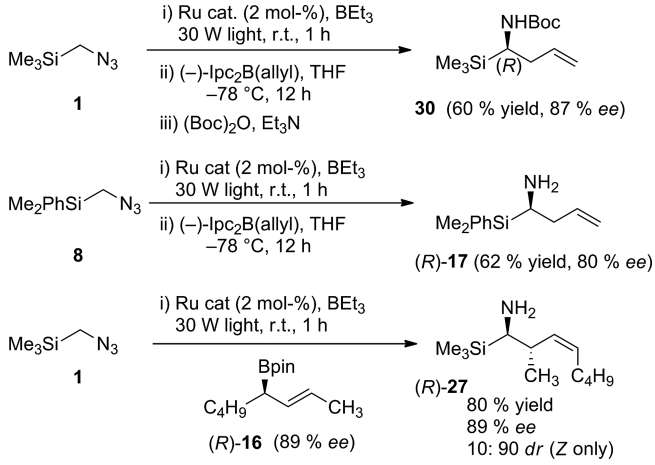
Table 1. Reaction scope.[a]



Entry	Azide	Boronate	Product	Yield[b] (*syn*/*anti*)[c]
1	**8**[13b]	**5**	 **17**	81 (–)
2	**9**[13b]	**5**	 **18**	69 (–)
3[d]	**1**	**10**	 **19**	67 (–)
4[d]	**8**	**10**	 **20**	80 (–)
5[d]	**9**	**10**	 **21**	85 (–)
6[e]	**1**	**11**	 **22**	69 (–)
7	**1**	**12**	 **23**	83 (95:5)
8	**1**	**13**	 **24**	82 (7:93)
9	**1**	**14**	 **25**	77 (7:93)
10	**1**	**15**	 **26**	76 (9:91)
11	**1**	*rac*-**16**	 **27**	71 (10:90)
12	**8**	**12**	 **28**	75 (94:6)
13	**8**	**13**	 **29**	83 (5:95)

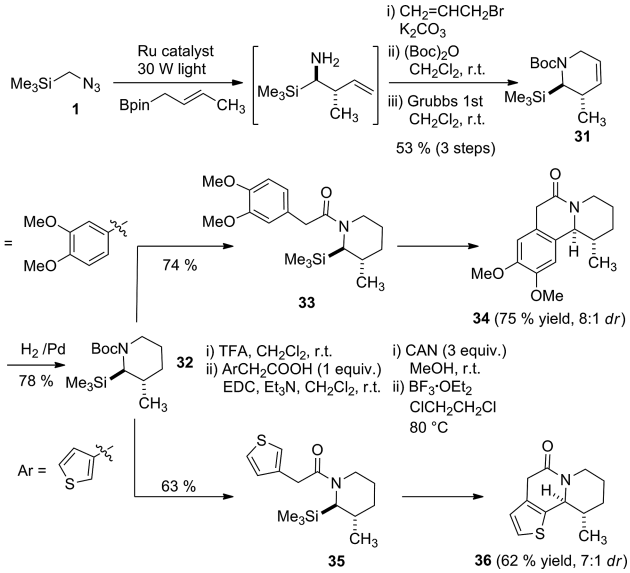
[a] Typical procedure: The substrate was treated with catalyst **2** (2 mol-%) and allyl- or allenylboronate (1.5 equiv.) in THF (0.5 M) under a 30 W fluorescent light. [b] Yield of isolated product. [c] The diastereomeric ratio was determined by analysis of the crude mixture by ^{1}H NMR spectroscopy. [d] A mixture of azide and allenylboronate (3 equiv.) was treated at 50 °C for 5 h. [e] The reaction was performed at 50 °C.

alized product (*R*)-**27** in over 80% yield with 10:90 selectivity. The fact that the *ee* of the product is 89% confirms the complete chiral transfer of allylic boronate **16**. Notably, three stereocenters (including olefin geometry) are generated in one step in an enantioselective and diastereoselective manner.



Scheme 3. Enantioselective synthesis of highly substituted α-silylamines.

The new synthesis of α-silylamines presented herein should find significant use in the synthesis of silicon-containing amines and azacycles. For example, highly functionalized piperidine ring *rac*-**31** could be obtained from azide **1** through the multistep synthesis shown in Scheme 4. Moreover, the silyl moiety in this compound can be used as a key element and enables further transformations in the late stage of the synthesis. To highlight this issue, we finally investigated the possibility of the oxidative cyclization of **32** to form a bicyclic piperidine ring, a motif found in numerous bioactive alkaloids. For this purpose, substrates **33** and **35** were prepared from key intermediate **32** in two steps



Scheme 4. Synthetic application; TFA = trifluoroacetic acid; EDC = 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide.

with no particular events. Initial tests on the direct oxidative Pictet–Spengler cyclization of **33** by using ceric ammonium nitrate (CAN) gave product **34** in low yield. Thus, indirect Pictet–Spengler reaction by way of the N,O-acetal intermediate was pursued.[19] This reaction gave desired product **34** in good yield over two steps with *trans* selectivity. Using the same protocol, amide **35** was converted into *trans*-bicyclic piperidine **36** in 62% yield.[20]

Conclusions

We developed a new stereoselective synthesis of α-silylamines from trialkylsilylmethyl azides. Even chiral α-silylamines possessing multiple stereocenters were accessed by this method. The synthetic utility of α-silylamines as a reactivity-driven diversity-generating element was demonstrated by the ceric ammonium nitrate mediated oxidative cyclization reaction. Developing a catalytic asymmetric version of the α-silylamine synthesis as well as expanding the synthetic application of α-silylamines is currently ongoing in our laboratory. The results of these studies will be reported in due course.

Experimental Section

Preparation of α-Silylamine 7: Ruthenium catalyst **2** (5.1 mg, 0.0050 mmol) was introduced into a flame-dried J Young flask filled with N_2 gas. Then, THF (0.25 mL) was added to the J Young flask under a stream of N_2 gas. The solution was stirred at room temperature without light for 10 min to dissolve **2**. Then, trimethylsilyl methyl azide (**1**; 32.3 mg, 0.250 mmol) in THF (0.25 mL) and allylboronic acid pinacol ester (**5**; 68.2 μL, 0.375 mmol) were added to the solution under N_2 gas flow conditions. The mixture was stirred at room temperature under a 30 W fluorescent light for 3 h. The reaction was quenched by adding $CHCl_3$ (1 mL), and the solution was stirred for 5 min. 1 N HCl was added to the solution until pH ≈ 1. The solution was washed with Et_2O (3× 5 mL) and neutralized with 6 N NaOH. The solution was extracted with Et_2O (5× 5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was dissolved in CH_2Cl_2 (5 mL, 0.05 M), and triethylamine (70 μL, 0.50 mmol) and *p*TsCl (71.5 mg, 0.375 mmol) were then added. The mixture was stirred at room temperature overnight. The reaction was quenched with H_2O (3 mL). The solution was extracted with CH_2Cl_2 (3 × 3 mL). The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel (hexane/EtOAc, 80:20) to give **7** as a white solid (61.7 mg, 0.208 mmol, 83%). R_f = 0.56 (hexane/EtOAc, 80:20). M.p. 109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 9 H), 2.01–2.24 (m, 2 H), 2.42 (s, 3 H), 2.89 (dt, J = 9.6, 2.6 Hz, 1 H), 4.31 (d, J = 9.6 Hz, 1 H), 4.77–4.88 (m 1 H), 4.93 (dt, J = 10.2, 0.9 Hz, 1 H), 5.53 (dddd, J = 17.1, 10.1, 7.8, 6.9 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.76 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –2.7, 21.7, 36.1, 43.7, 118.3, 127.5, 129.7, 135.1, 138.6, 143.4 ppm. IR: $\tilde{\nu}$ = 3273, 3071, 2958, 2893, 1640, 1597, 1496, 1321, 1252, 1162, 1094 cm^{-1}. HRMS (FAB+): calcd. for $C_{14}H_{24}NO_2SiS$ 298.1297 $[M + H]^+$; found 298.1299.

Supporting Information (see footnote on the first page of this article): General experimental remarks, detailed experimental procedures, and spectroscopic data for all compounds.

Acknowledgments

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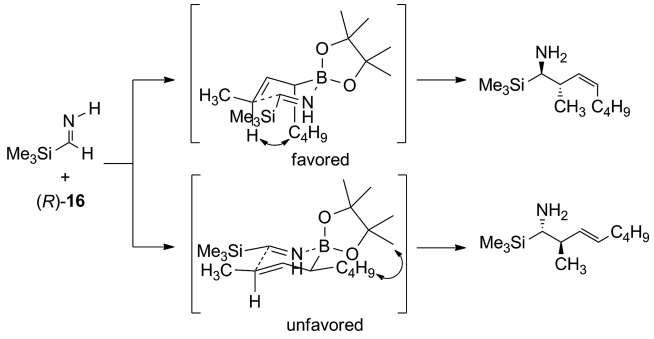
[14] For detailed information regarding structure determination, see the Supporting Information.
[15] The (*Z*) selectivity can be explained by the steric effect of the boronate ester moiety and the alkyl substituent on the boronate in forming the six-membered closed complex:



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[16] The absolute configuration was determined by conversion of **30** into known 2-trimethylsilyl-*N*-Boc-piperidine and by comparison of the specific configuration. For detailed information, see the Supporting Information. For a reference, see: D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* **2010**, *132*, 7260–7261.
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[19] H. Sun, C. Martin, D. Kesselring, R. Keller, K. D. Moeller, *J. Am. Chem. Soc.* **2006**, *128*, 13671–13771.
[20] The relative stereochemistry of bicyclic piperidines **35** and **37** was determined by analysis of the coupling constant (J = 12.5 Hz for the major isomer and J = 0 Hz for the minor isomer) in the ^{1}H NMR spectrum. For detailed information, see the Supporting Information.

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