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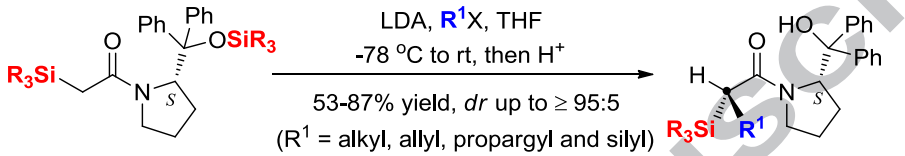

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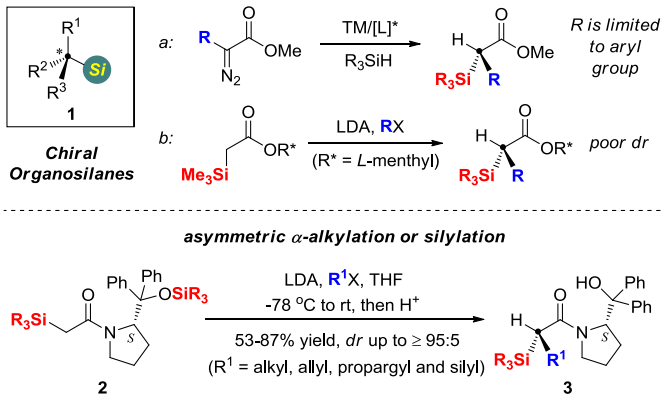
ABSTRACT

Asymmetric alkylation or silylation of (*S*)-(−)-diphenylprolinol-derived α-silyl amide has been developed to synthesize optically pure α-monosilyl or bis(silyl) amides in good yields with high diastereoselectivity.

Optically active *C*-centered chiral organosilanes **1**, in which the chiral center is adjacent to a silyl group, are useful synthons in organic synthesis.[1] The species can be converted into diverse chiral building blocks. For example, the steric effect of silicon has been utilized to create a new stereogenic center in the structure of **1** diastereoselectively.[2] By Fleming-Tamao oxidation, **1** (R^1 = H) can be transformed directly into chiral secondary alcohols with configurational retention.[3] The asymmetric Sakurai allylation of **1** (R^1 = vinyl) with aldehydes has been also used to generate chiral homoallylic alcohols.[4] The stereoelectronic effect of silicon ensures an efficient chirality transfer from the chiral allylsilane into the product.

Among various chiral organosilanes, α-silyl carbonyl compounds (**1**, R^1 = COR) possessing both silyl and carbonyl functional groups represent an attractive type of synthons. While these species can be synthesized enantioselectively by asymmetric insertion of diazoacetates into the Si-H bond, the α-substitution in diazoacetates are generally limited to aryl groups (Scheme 1, upper a).[5] Paquette et al. developed an asymmetric alkylation of α-silyl *L*-menthyl ester to generate chiral organosilane, but most of the cases only showed poor diastereoselectivity (Scheme 1, upper b).[6] It is noteworthy that amides containing a chiral amine as the auxiliary have shown a wide utility for obtaining a diastereoselective α-alkylation.[7] However, the process was used only in a few of examples to synthesize chiral α-silyl amides.[8] Herein we report that (*S*)-(−)-diphenylprolinol-derived α-silyl amide **2** proves being an valuable scaffold for the asymmetric alkylation or silylation, giving the optically pure α-monosilyl or bis(silyl) amides **3** in good yields with high diastereoselectivity (Scheme 1, lower).

Scheme 1. Previous Methods to Synthesize Chiral α-Silyl Carbonyl Compounds (Upper); Asymmetric Alkylation or Silylation to Form α-Monosilyl or Bis(silyl) Amides (Lower)



We initially examined synthesis of **3** via α-silylation of chiral amide **4**, which was prepared in 85% yield by *N*-acylation of (*S*)-(−)-diphenylprolinol with propanoic acid. While the lithium enolate of ester generally undergoes *O*-silylation to give silyl ketene acetal, silylation of the lithium enolate of amide can occur

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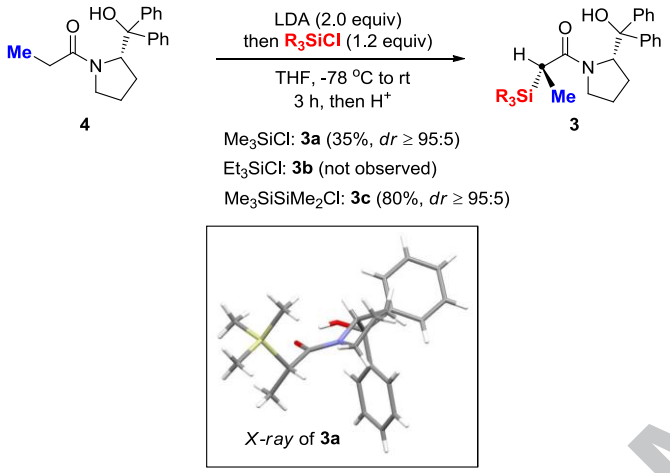
at the *C*- rather than *O*-position to give α-silyl amide regioselectively (Scheme 2).[9] As expected, treatment of **4** with LDA at -78 °C followed by silylation with 1.2 equiv of Me_3SiCl gave rise to the desired α-silyl amide **3a** as a single diastereomer, albeit in 35% yield. The stereochemistry of **3a** was ambiguously confirmed by its X-ray analysis.[10] No *O*-silylation was observed on both enolate and diphenylprolinol moieties. Recovery of 50% of amide **4** implied the low α-trimethylsilylation reactivity of its enolate. Silylation was even completely prohibited to form **3b** when using bulkier Et_3SiCl. Interestingly, despite Me_3SiMe_2SiCl is bulkier than both Me_3SiCl and Et_3SiCl, the corresponding α-silyl amide **3c** was obtained in a much higher yield of 80% with ≥ 95:5 *dr*.[11]

Scheme 2. Asymmetric α-Silylation of Amide 4 to Form 3



We next tested the feasibility of synthesizing chiral α-silyl amide by the process featuring silylation followed by alkylation (Scheme 3). In the presence of 2.5 equiv of Me_3SiCl, acetamide **5** underwent a dual silylation on its α-position (*C*-silylation) and the diphenylprolinol moiety (*O*-silylation) to give **2a** in 83% yield. α-Methylation of **2a** with MeI and the subsequent acidic work-up to remove the silyl group on the diphenylprolinol provided the α-silyl amide in 83% yield with ≥ 95:5 *dr*. This product shows the identical NMR spectral character to that of **3a** obtained by α-silylation of amide **4** (Scheme 2). In addition, reaction of Me_3SiMe_2Si-substituted **2b** generated the desired α-silyl amide **3d** in 30% yield as a single diastereomer, in which the Me_3SiMe_2Si group on the diphenylprolinol moiety was stable to the acidic work-up conditions. The bulky Me_3SiMe_2Si group might inhibit to a large extent the α-methylation of **2b**, leading to

Scheme 3. Asymmetric α-Methylation of Amide 2 to Form 3

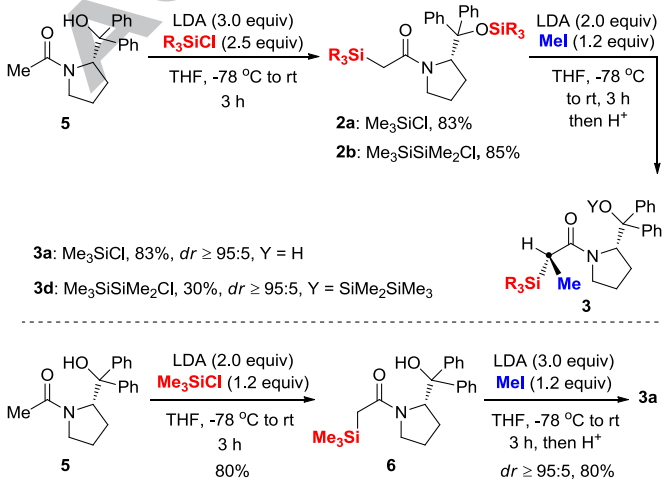
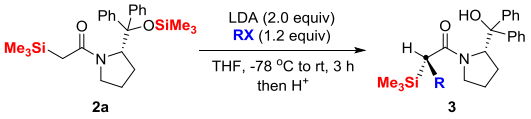
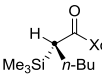
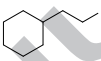
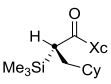
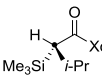
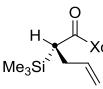
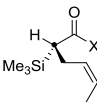
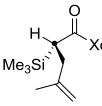
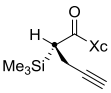
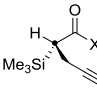
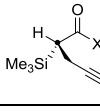


Table 1. Scope of Alkyl Halides.[a]



entry	RX	product		yield[b]	*dr*[c]
1			**3e**	81%	94:6
2			**3f**	63%	≥95:5
3			**3g**	83%	≥95:5
4			**3h**	87%	≥95:5
5			**3i**	85%	≥95:5
6			**3j**	80%	95:5
7			**3k**	78%	90:10
8			**3l**	53%	≥95:5
9			**3m**	N. R.	N. D
10			**3n**	77%	95:5
11			**3o**	73%	≥95:5
12			**3p**	58%	≥95:5

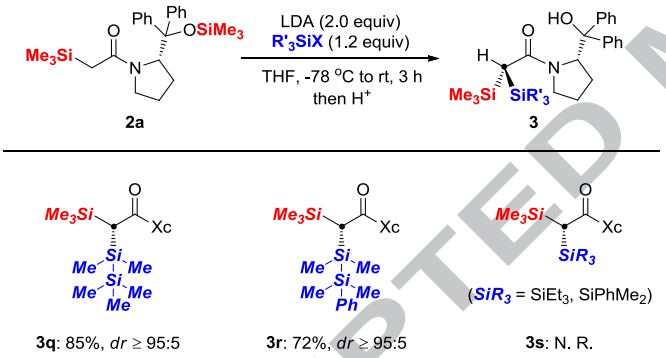
[a] Reaction conditions: **2a** (0.2 mmol), LDA (0.4 mmol) and RX (0.24 mmol) in THF at -78 °C to rt for 3 h. [b] Isolated yields after purification by silica gel column chromatography. [c] The ratios were determined by ^{1}H NMR spectroscopy of the crude products.

the low yield of **3d**. We also examined α-methylation of **6** containing a non-protected diphenylprolinol moiety. The

reaction gave **3a** in 80% yield with ≥ 95:5 *dr*. This result suggests that α-methylation of **2a** and **6** proceeds by the same stereochemical control. A one-pot synthesis of **3a** from **5** was carried out by sequential addition of Me_3SiCl and MeI. Unfortunately, the reaction only provided a complex mixture.

With the optimized reaction conditions in hands, the scope of the approach was next examined using **2a** with various alkyl halides. The approach was tolerated with unbranched *n*-butyl iodide and terminal BnO-substituted propyl iodide to give **3e** and **3f**, respectively, in good yields with high diastereoselectivity (Table 1, entries 1 and 2). Branched alkyl halides, in which the sterically demanding substituent is located either away from or closed to the electrophilic site, are also suitable substrates for the asymmetric α-alkylation to give **3g**-**3j** with high *dr* (entries 3-6). The results in entries 7-9 indicate a steric bias of allyl bromides for the efficiency of allylation. While using simple allyl bromide gave **3k** in 78% yield, the yield decreased to 53% when 3,3-dimethyl allyl bromide was used to generate **3l**. No allylation occurred with 2-methyl allyl bromide to form **3m**. The 2-methyl group, which is adjacent to the electrophilic α- and γ-positions, might inhibit the attack of the enolate of **2a**. In contrast, the reaction showed a good applicability to less sterically demanding propargyl bromides (entries 10-12). α-Silyl amides **3n**-**3p** were obtained in good yield with high *dr* by exclusive propargylation, rather than allenylation through a γ-substitution pathway.

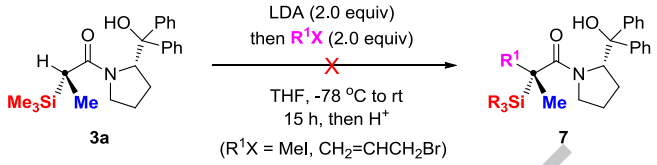
Scheme 4. Asymmetric α-Silylation of 2a to Form Chiral Geminal Bis(silanes) 3q and 3r



The process also provided an effective manner to construct structurally unique chiral geminal bis(silanes). These species contains two bulky silyl groups attached to one carbon center, making their synthesis kinetically and thermodynamically very challenging.[12] In the past few years, we have launched a series of studies on the synthesis and reactivity of geminal bis(silanes).[13] Those organosilanes generally possess two identical silyl groups, and hence they are achiral. To the best of our knowledge, little investigation has been made to construct the optically pure geminal bis(silanes),[14] which contain two different silyl groups and should have great synthetic potentials for the down-stream asymmetric transformations. As shown in Scheme 4, asymmetric α-silylation of **2a** with disilyl chloride gave rise to chiral geminal bis(silanes) **3q** and **3r** with ≥ 95:5 *dr* in 85% and 72% yield, respectively. We also tested the feasibility of installing others silyl groups into **2a**. However, neither Et_3SiCl nor $PhMe_2SiCl$ led to the desired α-silylation to form **3s**.[15] These results are consistent with the observation that Me_3SiMe_2SiCl is more reactive than Me_3SiCl for α-silylation, even though it is sterically bulkier (Scheme 2).

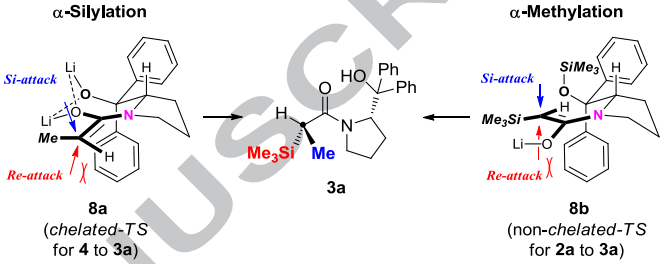
Further α-alkylation of **3a** would give rise to **7** containing a silicon-substituted quaternary carbon center. However, the

Scheme 5. Attempts to Form Quaternary Carbon-substituted 7 by Asymmetric α-Alkylation of 3a



reactions with either MeI or allyl bromide only led to recovery of **3a**; no desired alkylated product **7** was formed (Scheme 5). Probably, the bulky silyl group prohibits α-alkylation of **3a** to form the sterically congested quaternary carbon center.

Scheme 6. Models to Explain The Stereochemical Outcome



As shown in Schemes 2 and 3, α-silylation of **4** and α-methylation of **2a** provided the identical product **3a** as a single diastereomer. These results imply that the processes might proceed by two contrasting stereochemical courses. We assumed that while a chelated enolate **8a** might be involved in the silylation of **4**, a non-chelated enolate **8b** most likely dominates the methylation of the silyl-protected **2a** (Scheme 6).[16] In **8a**, the enolate moiety should adopt a *Z*-configuration to minimize the allylic strain between the α-methyl group and the pyrrolidine moiety.[17] Thus, silylation of the conformationally fixed **8a** from the less hindered *Si*-face would give **3a**. On the other hand, the enolate moiety in **8b** should also adopt a *Z*-configuration, but probably in a different orientation to minimize the non-bonded interaction with the diphenylprolinol moiety. This orientation allows the *Si*-face in **8b** sterically more accessible for methylation, affording **3a** predominantly.

In summary, we have described an efficient approach to synthesize optically pure organosilanes by asymmetric alkylation of (*S*)-(−)-diphenylprolinol-derived α-silyl amide. The approach has also shown a good applicability to construct the synthetically challenging chiral geminal bis(silanes) via asymmetric α-silylation. Further applications of this methodology are ongoing in our group.

Acknowledgments

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10. CCDC 1471145 [**3a**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
11. Currently, we do not know the exact reason why the bulkier Me_3SiMe_2SiCl shows a higher α-silylation reactivity than smaller Me_3SiCl. Probably, the electronic property of the Si-Si bond plays one of the important roles in this case. Previous studies have shown that the Si-H bond in R_3SiH can be dramatically weakened by successive substitution of the alkyl group with the silyl group, although the origin of this effect is unclear (See references below). We assumed that the Si-Cl bond in Me_3SiMe_2SiCl might be weakened by the similar effect, rendering Me_3SiMe_2SiCl more reactive than Me_3SiCl. In addition, due to the Si-Si bond (≈ 2.39 Å) is longer than the Si-C bond (≈ 1.93 Å), switching Me to Me_3Si group may not increase the steric effect as much as one expect. (a) Walsh, R. *Acc. Chem. Res.* **1981**, *14*, 246-252. (b) West, R. *Pure Appl. Chem.* **1982**, *54*, 1041-1050. (c) Sakurai, H. *Pure Appl. Chem.* **1987**, *59*, 1637-1946. (d) Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267-5268. (e) Shimizu, M.; Oda, K.; Bando, T.; Hiyama, T. *Chem. Lett.* **2006**, *35*, 1022-1023.
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Highlights

- (*S*)-(−)-diphenylprolinol is shown as an efficient auxiliary to ensure the high diastereoselectivity of alkylation.
- A range of optically pure chiral α-monosilyl amides were obtained in good yields with high diastereoselectivity.
- The approach is applicable to synthesize sterically congested chiral α-bis(silyl) amides.