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Asymmetric Synthesis of *N*-Boc-(*R*)-Silaproline via Rh-Catalyzed Intramolecular Hydrosilylation of Dehydroalanine and Continuous Flow *N*-Alkylation

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Supporting Information

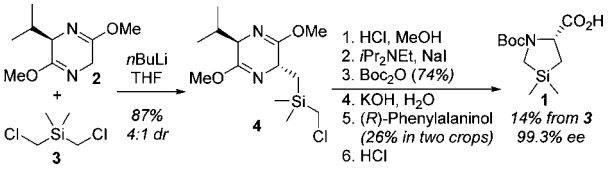
ABSTRACT: An asymmetric synthesis of a silicon-containing proline surrogate, *N*-Boc-(*R*)-silaproline (**1**), is described. Starting from *N*-Boc-dehydroalanine ester, deprotonation, followed by *N*-alkylation with chloromethyldimethylsilane under flow conditions, afforded the *N*-alkylated product **8** in 91% yield. An unprecedented enantioselective $(NBD)_2RhBF_4$/Josiphos 404-1 catalyzed 5-*endo-trig* hydrosilylation afforded the silaproline ester in 85−90% yield and >95% ee. Subsequent saponification and salt formation upgraded **1** to >99% ee.

Despite the burgeoning utility of silicon-containing amino acids in medicinally relevant compounds, their synthetic access remains challenging. To date, the preparation of these valuable chiral building blocks has required either auxiliary-controlled alkylation or classical/enzymatic resolution of racemic intermediates.[1] In this letter, we report the first catalytic asymmetric synthesis of a silicon-containing amino acid, utilizing a novel enantioselective rhodium-catalyzed hydrosilylation reaction to simultaneously set the desired stereochemistry and introduce silicon into the molecule.[2]

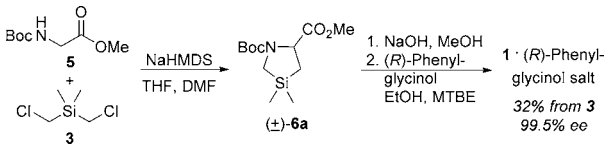
The dearth of asymmetric catalytic approaches to silicon-containing amino acids recently proved challenging in the context of a drug development program that required the preparation of *N*-Boc-(*R*)-silaproline (Sip, **1**). First synthesized by Cavelier and Tacke in 2000,[3] Sip has been shown to afford enhanced bioavailability and biological activity when acting as a replacement for natural proline in medicinally relevant compounds.[4−8] Our initial approach to this compound hewed closely to established methods[3] and proceeded in seven steps from Schöllkopf reagent (**2**) and bis(chloromethyl)-dimethylsilane (**3**), delivering compound **1** in 14% overall yield (Scheme 1).

Early efforts in our laboratories provided a significant improvement over the existing chemistry by employment of a *C*,*N*-dialkylation strategy. This approach delivered racemic ester **6a**, which, after hydrolysis and classical resolution as the (*R*)-phenylglycinol salt, afforded enantiopure Sip in 32% overall yield from starting materials **3** and **5** (Scheme 2). While this approach represented an improvement in yield and overall efficiency from the prior auxiliary strategy, it still suffered from the loss of more than half the desired product and required use of an expensive silane starting material.

Scheme 1. First Generation Synthesis of Sip (1)



Scheme 2. Second Generation Synthesis of Sip (1)



With focus toward solving each of these challenges, we evaluated a series of known asymmetric catalytic approaches to carbogenic non-natural amino acids.[9] Unfortunately, these methods all failed to provide a path forward to the desired silicon-containing amino acid. As a result, we turned our attention to an unprecedented hydrosilylation approach.[10] To date, this technology has not been employed to access silicon-containing amino acids, likely because the reaction typically proceeds through Si−H addition in a 1,2-fashion, delivering hydrogen to carbon and silicon to nitrogen. We envisioned that the requisite dehydroamino acid, a preeminent asymmetric hydrogenation substrate, would serve as the ideal starting point for our enantioselective hydrosilylation investigation. In a retrosynthetic sense, Sip **1** would arise from dehydroalanine **9** and chloromethyldimethylsilane (**10**). From these materials forward, either inter- or intramolecular hydrosilylation approaches would be feasible to establish the α-amino stereocenter (Scheme 3).

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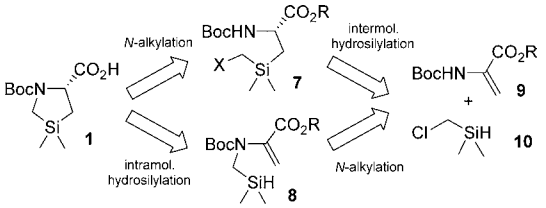
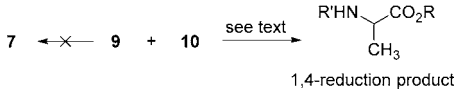
Scheme 3. Retrosynthetic Analysis of 1



Utilizing an intermolecular strategy, it was clear from the outset that the inherent electronic bias of these substrates could lead to undesired 1,4-reduction of the enoate acceptor, and the major observed product was simply the alkane (Scheme 4).[11]

Scheme 4. Attempted Intermolecular Hydrosilylation of 9 with 10



Hypothesizing that geometric constraints would have a significant impact on the regioselectivity of the reaction, we refocused our efforts on an intramolecular approach that would represent the first known hydrosilylation to set an amine stereocenter in a silicon-containing amino acid.[12]

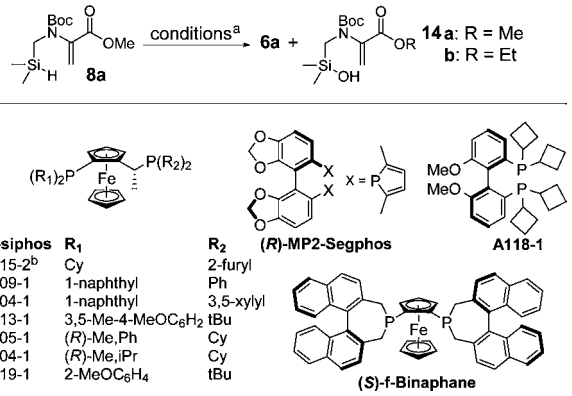
Our development of an intramolecular asymmetric hydrosilylation reaction began by studying the reactivity of silane-ligated olefin **8a**/**b** in the presence of a library of chiral phosphine bound transition metal complexes. Specifically, $(NBD)_2RhBF_4$, $(COD)Ru(Me\text{-}allyl)_2$, $[(allyl)PdCl]_2$, and $(COD)PtCl_2$ were evaluated with and without H_2 activation, as well as $[(COE)_2RhCl]_2$ and $[(COE)_2IrCl]_2$ with and without AgOTf activation. Consistent with our hypothesis, this intramolecular approach exhibited a strong preference for reversing the natural reaction selectivity, and we observed the desired carbon−silicon-bond product. Among the metal sources examined, rhodium was found to be the most promising in terms of conversion and enantioselectivity. From our chiral phosphine ligand library, (*R*)-MP2-SegPhos,[13] (*S*,*S*)-f-Binaphane,[14] and several Josiphos ligands[15] were found to afford the most reactive and selective catalysts (Table 1). Silanol **14a** was observed as the major byproduct and necessitated the employment of anhydrous reaction conditions to achieve high yields.[16] Minor amounts of 1,4-reduction product were also detected. Since Josiphos J404-1 is the most available among high-performing ligands, we focused on this ligand for the rest of the optimization.

A screen of 24 solvents[17] with Rh/J404-1 found DCE and CH_2Cl_2 were optimal solvents for the hydrosilylation reaction. Using chromatographically purified substrate **8a** and 3 mol % catalyst, the reaction was nearly complete in less than 5 min at room temperature, affording 91% product in 98.7% ee along with 6% unreacted starting material. Higher catalyst loadings (5 and 10 mol %) at two different concentrations led to lower conversions to the desired product, even at elevated temperatures (Table 2).[18]

To successfully apply our novel asymmetric catalytic hydrosilylation, it was critical to develop an efficient synthesis of dehydroalanine ester **8a**/**b**. *N*-Alkylation of dehydroalanine **9**[19,20] with silane **10**[21] proved challenging, as both the anion of **9** and silane **10** were shown to be unstable under the reaction conditions, and the union of these two fragments did not proceed sufficiently rapidly to overcome these inherent instabilities. After extensive evaluation, NaHMDS and DMF were found to be the optimal combination of base and solvent. However, even under these preferred conditions, yields of **8a**/**b** plateaued around 50−55% and 60−65% respectively, and attempts to purify compound **8** by silica gel chromatography resulted in significant hydrolysis to silanol **14**.

The yield of ene-silane **8** could be improved by changing the order of addition such that silane **10** was introduced to the pregenerated amide anion of **9**; however, on increasing the reaction scale from 1 to 40 g, a corresponding diminution of yield was observed. Careful profiling of the reaction determined that the anion of **9** was decomposing at a rate faster than that of the desired *N*-alkylation reaction, an observation that suggested the reaction performance would continue to worsen with increasing scale. As such, this reaction mode was deemed not

Table 1. Ligand Screen of Rh-Catalyzed Hydrosilylation

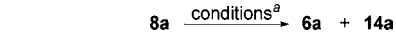


Josiphos	R_1	R_2
J215-2[b]	Cy	2-furyl
J409-1	1-naphthyl	Ph
J404-1	1-naphthyl	3,5-xylyl
J013-1	3,5-Me-4-MeOC_6H_2	tBu
J605-1	(*R*)-Me,Ph	Cy
J304-1	(*R*)-Me,iPr	Cy
J219-1	2-MeOC_6H_4	tBu

entry	ligand	% ee 6a[c]	6a[d]	14a[d]
1	(*R*)-MP2-Segphos	98.9	39	20
2	J215-2	−98.6	44	28
3	J409-1	−98.0	67	7
4	J404-1	−96.6	58	7
5	A118-1	91.8	80	6
6	(*S*,*S*)-f-Binaphane	89.5	73	6
7	J013-1	88.5	56	5
8	J605-1	87.4	34	22
9	J304-1	−86.1	50	15
10	J219-1	83.1	53	12

[a]Conditions: 4 μmol (1 mg) scale, 10% $(NBD)_2RhBF_4$/168 chiral ligands, DCE, 0.08 M, 60 °C. [b]Absolute configuration of ligand is opposite of the drawn structure. [c]Determined by chiral HPLC analysis. Postive values denote (*S*)-product. [d]HPLC area percent.

Table 2. Rh Catalyst Loading Study



concn	loading	% ee 6a[b]	6a[c]	14a[c]	8a[c]
0.08 M	10%	−95.1	67	3	30
	5%	−98.1	74	8	18
	3%	−98.3	89	4	7
0.2 M	10%	−98.1	68	3	28
	5%	−98.8	74	8	17
	3%	−98.7	91	3	6

[a]Conditions: 8−20 μmol (2.2−5.5 mg) scale, 3−10% $(NBD)_2RhBF_4$/J404-1, DCE, 0.08 or 0.2 M, 100 °C. [b]Determined by chiral HPLC analysis. [c]HPLC area percent.

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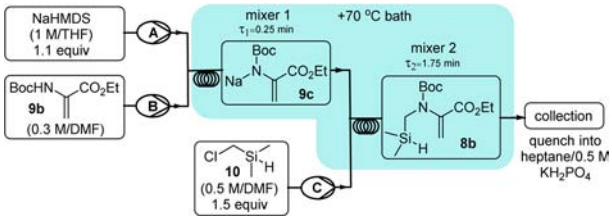
viable as a cornerstone of the synthetic approach to amino acid **1**.

Given the mechanistic understanding obtained from this anion chemistry in batch mode, we thought higher yields should be achievable by running the reaction in flow with a fast mixing time.[22] This hypothesis proved correct, and the reaction yield increased with an increase in temperature and decrease in residence time. We identified optimized conditions that achieved 95% conversion and 91−94% assay yield (Table 3, entry 8) of silane **8b**. A 0.3 M solution of **9b** in DMF was treated with 1.1 equiv of 1 M NaHMDS/THF at 70 °C for 0.25 min. The resulting anion **9c** was combined with 1.5 equiv of silane **10** in DMF (0.5 M) at 70 °C for 1.75 min. The reaction stream was quenched into a cold mixture of heptane and 0.5 M KH_2PO_4. The heptane layer was washed with water and dried azeotropically to afford crude **8b** as an oil, which was used directly in the hydrosilylation.

Table 3. Optimization of Flow Chemistry to 8b

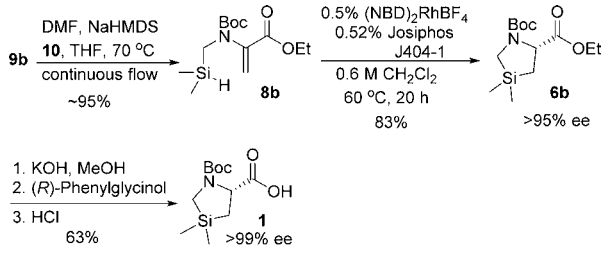


entry	temp (°C)	total τ (min)	conv (%)	yield (%) of **8b**
1	23	2	4	n.d.
2	23	4	30	n.d.
3	23	8	50	n.d.
4	23	15	70	n.d.
5	23	30	88	70
6	50	15	90	77
7	50	5	95	86
8	70	2	95	91
9	70	1	77	76

Use of crude **8** was critical to develop a streamlined synthesis of Sip; unsurprisingly, the presence of any associated impurities in the crude reaction stream resulted in a significant retardation in the rate of hydrosilylation. Under optimized conditions, operating at 60 °C in DCE or CH_2Cl_2, with 0.5 mol % catalyst, resulted in >95% conversion to the desired amino acid **6b**, with 83−89% solution yield and the critical high enantioselectivity at 95−99% ee.

To isolate pure **1**, the reaction mixture from the hydrosilylation was concentrated, and crude **6b** was subjected to saponification with either KOH/MeOH or LiOH/THF to afford the desired acid **1** in 87% yield. This material was isolated as the (*R*)-phenylglycinol salt that served to upgrade the chemical and enantiomeric purity to >95% and 99% ee, respectively. After the salt break, free acid **1** was obtained in comparably high purity. Ultimately, our asymmetric catalytic synthesis provided *N*-Boc-(*R*)-Sip (**1**) in three steps with salt formation/salt break, >99% ee, and 50% overall yield (Scheme 5).

Scheme 5. Synthesis of Sip 1 via Intramolecular Hydrosilylation



In summary, we have reported the first catalytic asymmetric synthesis of a silicon containing amino acid, *N*-Boc-(*R*)-Sip (**1**). The critical α-amino stereocenter was established through an unprecedented, enantioselective Rh-catalyzed intramolecular hydrosilylation reaction that simultaneously formed a necessary carbon−silicon bond.[23] The route was rendered efficient and scalable through the development of a continuous flow *N*-alkylation of the readily available dehydroalanine precursor. Ultimately, the combination of these two discoveries afforded silaproline **1** in a mere three steps and salt formation/salt break. Work to understand the scope and mechanism of the asymmetric hydrosilylation reaction further is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00548.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(11) (a) Our initial investigations of the intermolecular hydrosilylation employed conditions similar to those for the intramolecular screens described in the text and found very low reactivity even at 10% catalyst loading and 60 °C, affording mostly unreacted starting materials along with minor 1,4-reduction product. (b) After completion of this work, G. Persanti et al. reported a racemic synthesis of silicon-containing amino acids through copper-catalyzed conjugate additions to dehydroalanine derivatives: Bartoccini, F.; Bartolucci, S.; Lucarini, S.; Piersanti, G. *Eur. J. Org. Chem.* **2015**, *2015*, 3352−3360.
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(20) (a) **9a**/**b** are highly prone to polymerization as neat oils even at −20 °C. Improved stability of **9** was achieved by storing as a 0.9 M DMF solution (∼4 vol DMF) with 0.1 wt % 4-methoxyphenol or 2,6-di-*tert*-butyl-4-methoxyphenol. The concentration of **9** in this solution was unchanged for at least 5 months after multiple 5−25 °C cool−heat cycles. (b) Levy, L. B. *Process Saf. Prog.* **1993**, *12*, 47−48.
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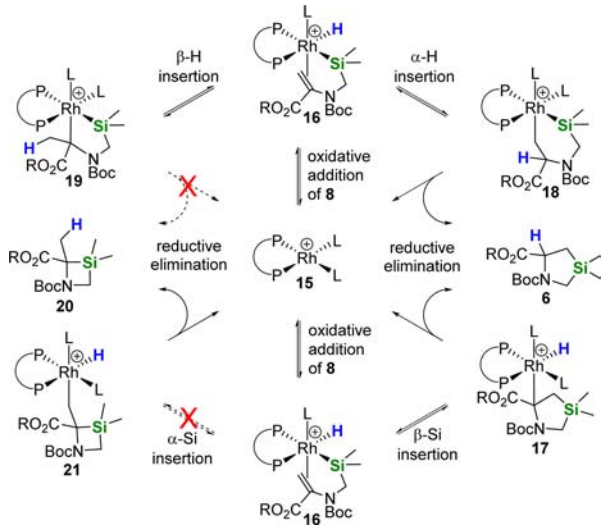
(23) Possible reaction pathways are depicted below; L may be solvent, NBD, or a coordinating group on the substrate in analogy to rhodium-catalyzed asymmetric hydrogenation. After oxidative addition **8** + **15** → **16**, the catalytic cycle may proceed via insertion of either Si or H into either the α- or β-carbon of the olefin. The desired product is formed in the case of β-Si insertion and reductive elimination **16** → **17** → **15** + **8** and in the case of α-H insertion and reductive elimination **16** → **18** → **15** + **8**. The process of β-H insertion **16** → **19** may occur; however, subsequent reductive elimination **19** → **15** + **20** is unlikely due to the ring strain of **20** and was never observed experimentally. Since all steps in catalytic hydrosilylation prior to reductive elimination are believed to be reversible, any **19** formed will equilibrate back to **16** and eventually form product. Similarly, the α-Si insertion **16** → **21** is also precluded by ring strain. For these reasons, tethering the silane to the alkene prevents the 1,4-reduction observed in intermolecular reactions.



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