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Enantioselective Bromo-oxycyclization of Silanol

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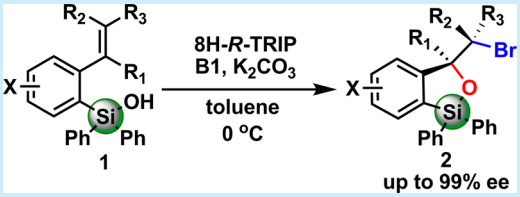
Supporting Information

ABSTRACT: Relying on the nucleophilicity of silanol for building up silicon-incorporated scaffold with an enantiopure tetrasubstituted carbon center remains elusive. In this report, asymmetric bromo-oxycyclization of olefinic silanol by using chiral anionic phase-transfer catalyst is described. This protocol provided a facile entry to a wide arrangement of enantiopure benzoxasilole in moderate to excellent enantioselectivities depending on the unique reactivity of bromine/*N*-benzyl-DABCO complex.



Organosilicon has undoubtedly occupied a unique position in organic chemistry, as shown by its wide applications in synthetic chemistry,[1a,b] material chemistry,[1c,d] and pharmaceutical chemistry.[1e] Therefore, an enormous endeavor has been dedicated to the incorporation of silicon into an organic scaffold, particularly into the enantiopure molecules, as the resulting organosilicon could be employed to construct diversely valuable chemical bonds (e.g., C−C, C−O, C−X bonds).[2] In this regard, although silanol is easily accessible and widely employed in synthetic chemistry (e.g., for the synthesis of siloxane,[1c] cross-coupling[2d]), harnessing the nucleophilicity of silanol for organic transformations is not well investigated, presumably due to its instability (easy to dehydrate to form siloxanes) and weak nucleophilicity of hydroxyl.[3] In this account, catalytic asymmetric reactions by directly taking advantage of silanol as oxygen source are scarce.[4] Only iridium- and palladium-catalyzed asymmetric allylic etherification of silanol has been reported by Hartwig and Xu respectively (Figure 1).[4a,b] However, silanol is only used as a water surrogate in those reactions, and the synthetic potential of silicon could not be fully utilized for constructing other chiral scaffolds in subsequent transformations. To this end, construction of an asymmetric tetrasubstituted carbon center directly based on the nucleophilicity of silanol represents a big challenge in the chemistry of silanol, which to the best of our knowledge has not been described to date.

Recently, asymmetric electrophilic halo-functionalization of unsaturated C−C bonds has witnessed great advances.[5,6] In this context, asymmetric halo-oxycyclization of olefinic alcohol has been extensively studied for giving easy access to enantiopure halogenated tetrahydrofuran and tetrahydropyran (Figure 1).[6] Furthermore, by employing tethered nucleophiles other than alcohol, asymmetric halo-oxycyclization has also emerged as

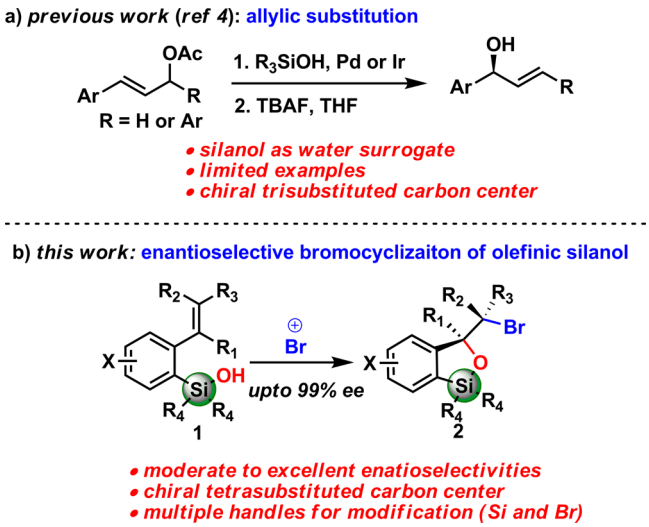


Figure 1. Enantioselective reactions directly relying on the nucleophilicity of silanol.

powerful strategy for construction of other functionalized chiral heterocycles.[6g−l] Despite the significant progress in asymmetric halo-oxycyclization reactions, synthetic applications of those enantiopure halogenated products are mainly limited to the derivatization of halogen. Therefore, incorporation of other orthogonally versatile functionality (e.g., Si, B) via asymmetric halogenation reaction is still highly desirable. In continuation of our work on asymmetric halogenation reactions,[7] herein we report our preliminary results on the first enantioselective

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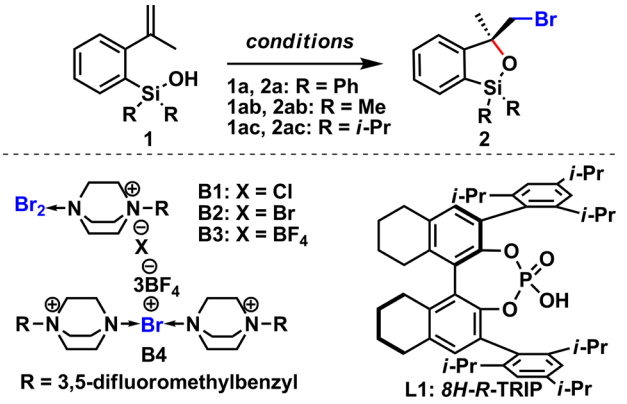
bromo-oxycyclization of olefinic silanol,[3b] which enables access to chiral benzoxasilole in moderate to excellent enantioselectivities.

The reaction condition optimization commenced with asymmetric bromocyclization of silanol **1a** using chiral anionic phase-transfer catalyst,[8] and selected results are listed in Table 1. Encouragingly, benzoxasilole **2a** was initially obtained in 82%

Table 1. Screening of Reaction Conditions for Enantioselective Bromo-Cycloetherification of Olefinic Silanol 1a[a]



entry	cat.	Br+	base	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	L1	B1	$NaHCO_3$	toluene	6	81	92
2	L1	B2	$NaHCO_3$	toluene	12	64	81
3	L1	B3	$NaHCO_3$	toluene	12	40	75
4	L1	B4	$NaHCO_3$	toluene	12	0	NR
5	L1	B1	$NaHCO_3$	hexane	20	53	93
6[d]	L1	B1	$NaHCO_3$	bezene	4	61	91
7	L1	B1	$NaHCO_3$	Et_2O	5	66	91
8	L1	B1	Na_2CO_3	toluene	4	81	95
9	L1	B1	K_2CO_3	toluene	4	87	95.5
10[d]	L1	B1	K_3PO_4	toluene	4	77	94
11[e]	L1	B1	K_2CO_3	toluene	20	80	94
12[f]	L1	B1	K_2CO_3	toluene	4	91	72
13[g]	L1	B1	K_2CO_3	toluene	4	89	68

[a]The reaction was carried out by addition of silanol **1a** (0.1 mmol) in toluene (1 mL) to a mixture of catalyst (0.01 mmol), brominating reagent (0.13 mmol), and base (0.40 mmol) in toluene (1 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC on a Chiralpak AD-H column. [d]The reaction was carried out at rt. [e]The reaction was conducted at −20 °C. [f]Silanol **1ab** as substrate. [g]Silanol **1ac** as substrate.

yield and 92% ee under our previous optimal conditions for asymmetric bromocyclization of tryptamine[7a] (entry 1). Subsequent evaluation of different bromine/*N*-benzyl-DABCO complexes showed that enantioselectivity of this reaction greatly depended on the counteranion of those complexes. **B1** with chloride as counteranion was superior to other bromine complexes in terms of yield and enantioselectivity (entries 2 and 3). To our surprise, bromonium salt **B4**[8d] was ineffective for this reaction even after the reaction time was extended (entry 4). This could be ascribed to the reduced reactivity of bromine by double complexation with *N*-benzyl-DABCO. Next, a survey of different chiral phosphoric acids revealed that 8*H*-*R*-TRIP **L1** was the catalyst of choice (see the Supporting Information). Solvent screening showed that inferior results were produced using nonpolar solvents other than toluene (entries 5−7). Among bases tested for this reaction, K_2CO_3 gave the best outcome, leading to **2a** in 95.5% ee (entries 8−10). Furthermore, reducing the temperature was detrimental to the reaction (entry 11). Two phenyls on silicon were indispensible for this reaction, as putting other substituents (e.g., Me, *i*-Pr) on silicon only led to the corresponding benzoxasiloles in moderate enantioselectivities (**2ab**, **2ac**, entries 12 and 13).

With optimal reaction conditions being set up, we turned our attention to examine the substrate scope of this reaction. Electron-donating or electron-withdrawing groups on phenyl have little impact on this reaction, leading to the corresponding benzoxasilole in excellent enantioselectivities (Figure 2, 92−97% ee, **2a**−**g**). However, presumably due to steric repulsion, introducing substituents adjacent to silicon dramatically reduced enantioselectivity of this reaction, leading to **2h** and **2i** only in 75% ee and 84% ee, respectively. On the other hand, substituents on olefin have complicated effect on enantioselectivities. Replacement of the olefinic methyl with other alkyl groups (e.g., Et, *i*-Pr) resulted in decreased enantioselectivities (87% for **2j** and 59% ee for **2k**). Only *6-endo*-bromooxycylization was detected when this methyl group was removed from the substrate, delivering benzoxasiline **2′l**[9] and **2′m** in moderate enantioselectivities. Substituents on the

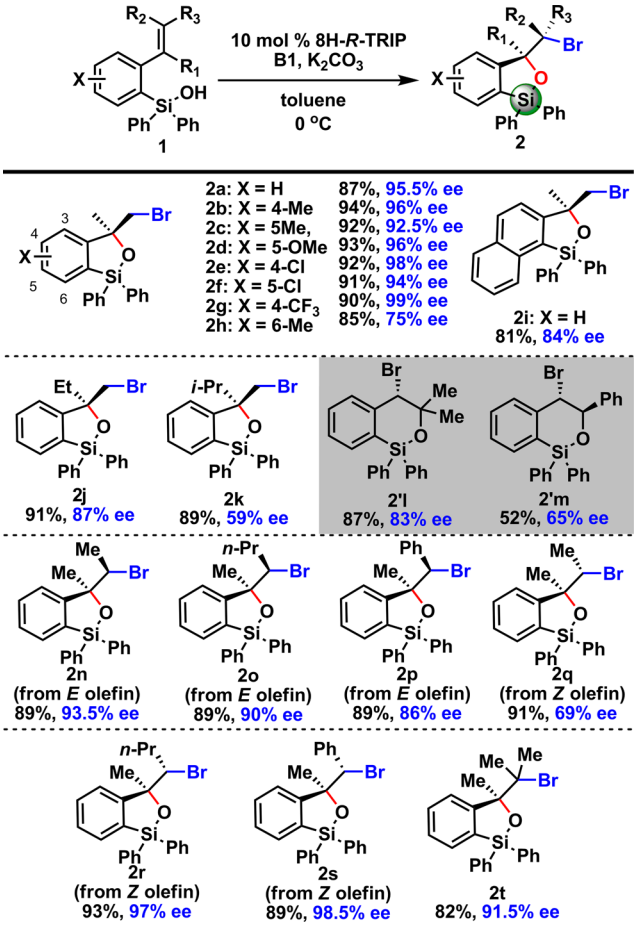


Figure 2. Substrate scope of enantioselective bromo-cycloetherification of olefinic silanols. Key: (a) The reaction was carried out by addition of silanol (0.1 mmol) in toluene (1 mL) to a mixture of 8*H*-*R*-TRIP (0.01 mmol), **B1** (0.13 mmol), and K_2CO_3 (0.40 mmol) in toluene (1 mL) at 0 °C.

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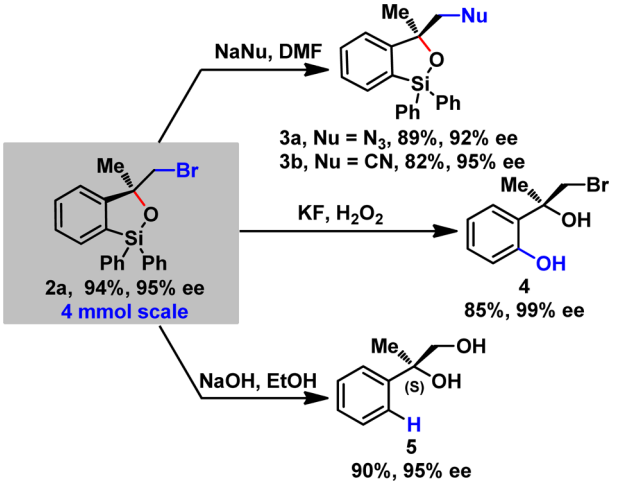
terminal olefin were also tolerated, while enantioselectivities depended on the configuration of alkene. As shown in Figure 2, lower enantioselectivities were obtained when the more bulky group was present on *E*-olefins (93% ee for **2n** to 86% ee for **2p**), while a reverse trend was observed for *Z*-olefins (69%ee for **2q** to 98.5% ee for **2s**). Finally, even tetrasubstituted olefin could be smoothly transferred to benzoxasilole **2t** in 91% ee.

To display the synthetic application of the resulting chiral benzoxasilole, synthesis of **2a** on a 4 mmol scale was first implemented to afford benzosilole in comparable enantioselectivity (Scheme 1). Its subsequent transformations by taking

Scheme 1. Synthetic Transformations of Benzoxasilole 2a

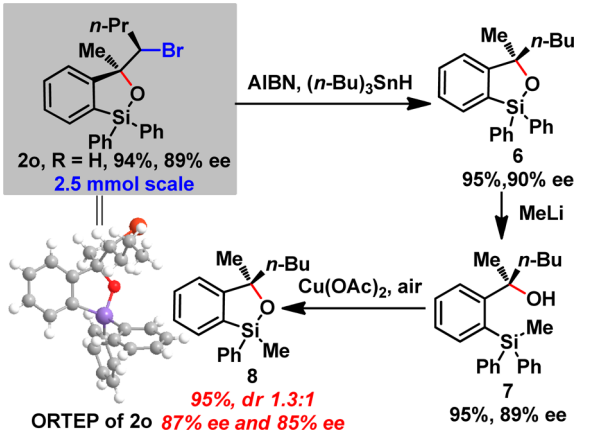


advantage of bromine and silicon were tested, respectively. Halogen as a handle for introduction of other functionality was routinely achieved by substituting of bromide with azide and cyanide, respectively, affording the corresponding benzosiloles **3a** and **3b** in high enantiopurities. For transformation of silicon, Tamao−Fleming oxidation of **2a** smoothly furnished phenol **4** with retention of bromine. Protonation of silicon concurrently with displacement of bromine with H_2O could be readily realized by heating **2a** in NaOH/EtOH, affording the known diol **5**, which established absolute configuration of **2a** to be *S*.[10]

Although benzoxasilole has emerged as an efficient transfer reagent for reactive organometallic reagents for cross-coupling reactions,[11] diastereoselective transmetalation of substituents on silicon for construction of stereogenic silicon is not well explored.[12] To this end, synthesis of **2o** on a 2.5 mmol scale enabled us to obtain a good crystal of **2o** for X-ray analysis, which confirmed its absolute configuration (Scheme 2).[13] Removal of bromine with AIBN/Bu_3SnH followed by ring opening of benzoxasilole with methyllithium generated silane **7** in excellent yields. Selective transfer of one phenyl of **7** proved to be challenging owing to the competitive transfer of methyl under previous cross-coupling conditions[11c,d] (see the Supporting Information). After extensive optimization (see the Supporting Information), transfer of methyl could be totally suppressed using CuI-catalyzed oxidative homodimerization of silane **7**.[14] Disappointingly, only poor diastereoselectivities resulted, and initial attempts employing achiral or chiral ligands proved to be fruitless (see the Supporting Information).

In conclusion, the generation of a chiral tetrasubstituted carbon center by directly utilizing the nucleophilicity of silanol is described. The reaction was realized by employing bromine/*N*-benzyl-DABCO complex under chiral anionic phase-transfer

Scheme 2. Selective Transmetalation of Phenyl on Silicon



catalyst. Structurally diverse benzosiloles were obtained in moderate to excellent enantioselectivities, which mainly depended on the substituents and configuration of alkene. Selective transfer of the phenyl of silane derived from chiral benzoxasilole was enabled by copper-catalyzed oxidative dimerization, albeit with no diastereoselectivity on the silicon stereogenic center.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03303.

Experimental procedures, spectral data, and copies of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(9) The absolute configuration of **2′l** was established by vibrational circular dichroism (VCD) studies. See the Supporting Information for detailed experimental data.

(10) The optical rotation of diol **5** ($[\alpha]^D$ = 11.4 (*c* 0.4, $CHCl_3$)) is in agreement with reported data of the (*S*)-isomer ($[\alpha]^D$ = 9.8 (*c* 0.4, $CHCl_3$)); see: Gaul, C.; Scharer, K.; Seebach, D. *J. Org. Chem.* **2001**, *66*, 3059 The rationale for the observed stereoselectivity was also proposed in the Supporting Information..

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(14) Biphenyl was detected as the dimerization product (see the Supporting Information). For selected examples of oxidative dimerization of arylsilane as a side reaction in cross-coupling reactions, see: (a) Funaki, K.; Kawai, H.; Sato, T.; Oi, S. *Chem. Lett.* **2011**, *40*, 1050. (b) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *J. Am. Chem. Soc.* **2014**, *136*, 254.

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