Chiral Organosilanes

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Asymmetric Synthesis of Chiral Silacarboxylic Acids and Their Ester Derivatives**

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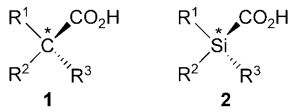
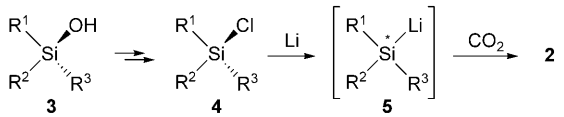
Chiral nonracemic carboxylic acids **1** with a stereogenic center at the α position are a prolific structural motif in basic life processes within organisms, and are important chiral building blocks or asymmetric reagents in the field of organic synthesis. Therefore, naturally occurring chiral carboxylic acids, as well as numerous artificial derivatives, have been synthesized and studied from a variety of viewpoints in organic chemistry and bioorganic chemistry.[1] Accordingly, their silyl analogues (**2**)[2] are highly attractive because of the potential reactivity as well as the unique physical properties of functional organosilanes. However, the asymmetric synthesis of chiral organosilanes[3,4] has presented significant challenges that have limited the development of viable synthetic methods for **2**.



1 **2**

We recently reported the successful asymmetric synthesis of chiral silanols **3** from the enantioselective nucleophilic substitution reaction of cyclic dialkoxysilanes; this synthesis involved an alkyllithium-mediated desymmetrization reaction in the presence of a chiral coordinating agent.[5] The remarkable efficiency of this method for enantiomerically enriched silanols **3** prompted us to develop a synthetic route to **2**, starting from **3**. We envisaged that chiral silacarboxylic acids **2** could be obtained from the carboxylation[6] of chiral silyllithium compounds **5**, themselves generated by the reductive lithiation of chiral chlorosilanes **4**, which could be prepared from chiral silanol **3** (Scheme 1). It is known that the stereoselectivity of the reductive lithiation of chiral chlorosilanes is significantly influenced by the steric demands of the substituents around the silicon atom.[7,8] Therefore, the judicious choice of substituents on the silicon atom was crucial for attaining high stereospecificity over the series of transformations in our synthetic strategy.



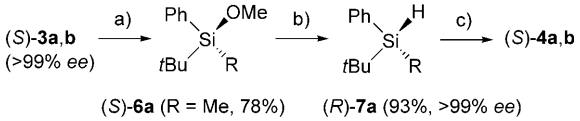
3 **4** **5**

2a, **3a**, **4a**, **5a**: R^1 = Ph, R^2 = *t*Bu, R^3 = Me
2b, **3b**, **4b**, **5b**: R^1 = Ph, R^2 = *t*Bu, R^3 = *n*Bu

Scheme 1. Strategy for the asymmetric synthesis of chiral silacarboxylic acid.

Gratifyingly, we found that chiral silyllithium compounds **5a**,**b**, derived from **3a**,**b**, underwent smooth carboxylation upon treatment with carbon dioxide to furnish **2a**,**b** in a highly stereospecific manner. We also found that the Mitsunobu-type reactions of **2a**,**b** with a variety of alcohols efficiently provided novel silacarboxyesters. Herein, we report the asymmetric synthesis of chiral silacarboxylic acids and their derivatives from chiral silanols **3**.

Our initial experiments focused on the stereoselective direct chlorination of silanols (*S*)-**3a** (>99% *ee*) and (*S*)-**3b** (>99% *ee*). Despite testing a variety of reagents for this transformation, including thionyl chloride,[9] we were unable to obtain the desired chlorosilanes **4a**,**b**, even under harsh conditions, which was possibly due to the severe steric congestion around the silicon center in silanols **3a**,**b**. We then turned our attention to consider stepwise procedures, including the radical-mediated chlorination of hydrosilanes (Scheme 2). First, the methyl etherification and subsequent $LiAlH_4$ reduction of silanols (*S*)-**3a** and (*S*)-**3b** led to the formation of the requisite hydrosilanes **7a** (R = Me) and **7b** (R = *n*Bu), respectively, whose enantiomeric excesses were



(*S*)-**6a** (R = Me, 78%) (*R*)-**7a** (93%, >99% *ee*)
(*S*)-**6b** (R = *n*Bu, 90%) (*R*)-**7b** (98%, >99% *ee*)

Scheme 2. Preparation of nonracemic chiral chlorosilanes **4**: a) MeI, KH, DMF, RT; b) $LiAlH_4$, Et_2O, reflux; c) $(PhCO_2)_2$ (10 mol%), CCl_4, reflux. DMF = *N*,*N*-dimethylformamide.

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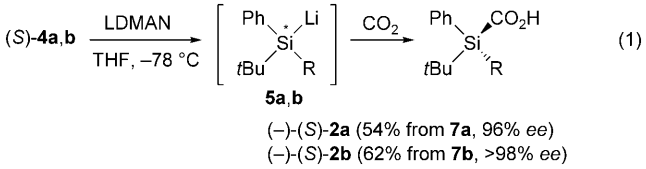
unambiguously determined to be >99% using chiral HPLC analysis. Although their absolute configurations are still to be confirmed, we believe that these two-step reactions both proceeded in a highly retentive fashion to give (*R*)-hydrosilane products, as previously demonstrated in the reaction of chiral methoxysilanes with $LiAlH_4$ in acyclic ether.[10] Second, optically pure **7a** and **7b** were chlorinated using modified literature conditions[11] to afford chiral chlorosilanes **4a** and **4b**, respectively, which were reduced directly without isolation to generate silyllithium compounds **5a**,**b**.

Reduction of crude **4a**,**b** was performed by treatment with excess lithium 1-(dimethylamino)naphthalenide (LDMAN)[12,13] in tetrahydrofuran. After stirring at −78 °C for 1 h, the mixture was bubbled with dried carbon dioxide followed by acidification to afford silacarboxylic acids **2a** and **2b**, both of which gave negative values for their optical rotation [Eq. (1)]. The enantiomeric excesses of **2a** and **2b**

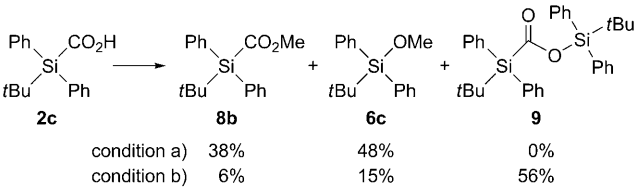


(1)

were successfully determined by chiral HPLC analysis to be 96% and >98% *ee*, respectively.[14] These results demonstrate that the sterically bulky substituents around the silicon atom contribute to the high stereospecificity.

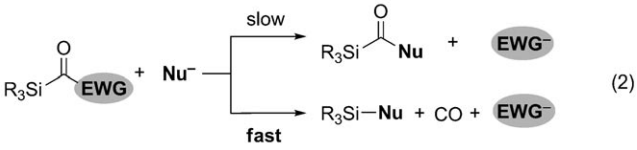
Novel chiral silacarboxylic acids **2a** and **2b** have comparable stereochemical stability to chiral carboxylic acids **1**; that is, nonracemic samples **2a** and **2b** showed no deterioration of their optical purity after refrigeration for one year (0 °C) under an argon atmosphere.[15] Moreover, the Mitsunobu-type reaction of (*S*)-**2a** with 9-anthracene methanol smoothly afforded crystalline ester **8a**. Crystals suitable for X-ray diffraction were obtained, which revealed the absolute stereochemistry of **8a**;[16,17] this result is significant considering the limited understanding of sila-stereochemistry (Scheme 3).[18] Considering that the chlorination of chiral hydrosilanes is known to be a retentive process,[11c] we concluded that the reduction of **4** and subsequent carboxylation may have overall retention of configuration.

It is worth noting that the preparation of silacarboxyesters from silacarboxylic acids, by routes other than the described Mitsunobu-type reaction,[19] is particularly challenging. Indeed, various conventional procedures for the dehydrative condensation reaction of carboxylic acids and alcohols, in which the carboxylic acid carbonyl moiety is electrophilically activated, were unsuitable for the comparable condensation of silacarboxylic acid **2c** with a variety of alcohols.[20] For example, Fischer esterification of achiral silacarboxylic acid **2c** in methanol, in the presence of a catalytic amount of sulfuric acid, gave a substantial amount of methyl ether **6c** (48%) in addition to the desired methyl ester **8b** (38%; Scheme 4). Moreover, DCC-mediated condensation of **2c**



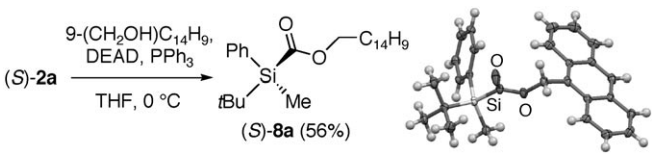
Scheme 4. Methyl esterification of silacarboxylic acid **2c**: a) cat. H_2SO_4, MeOH, reflux; b) MeOH, DCC, cat. DMAP, CH_2Cl_2, RT. DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

with methanol afforded unexpected silacarboxylic acid silyl ester **9** (56%)[21] in addition to **8b** (6%) and **6c** (15%). Therefore, we tentatively conclude that an electrophilically activated silacarbonyl intermediate bearing an electron-withdrawing group (EWG) prefers decarbonylation to nucleophilic attack at the carbonyl carbon [Eq. (2); Nu = nucleophile].



(2)

Intrigued by the distinctive reactivity of these silacarboxylic acids, we performed density functional theory (DFT) calculations and natural bond orbital (NBO) analysis on pivalic acid (**1a**) and trimethylsilylcarboxylic acid (**2d**), to make a comparison of the reactivity between structurally simple carboxylic acids and silacarboxylic acids;[22,23] their representative atomic charges and unoccupied orbitals are shown in Figure 1. Notably, the atomic charge at the silicon atom (+1.623) of **2d** is more positive than that at the carbonyl carbon (+0.431), in sharp contrast to **1a**, which has an α carbon that is less-positive (−0.189) than the carbonyl carbon (+0.831). Furthermore, both the LUMO+1 (Si–C σ*



Scheme 3. Esterification of (*S*)-**2a** and the molecular structure of ester (*S*)-**8a** (ellipsoids set at 40% probability level). DEAD = diethyl azodicarboxylate.

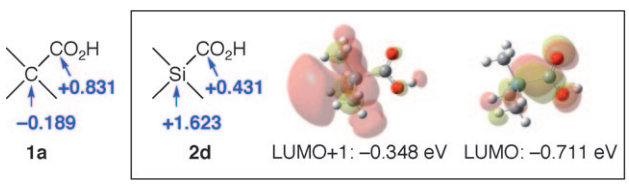


Figure 1. DFT calculation and NBO analysis of carboxylic acids **1a** and **2d**. LUMO = lowest unoccupied molecular orbital.

orbital) and the LUMO (carbonyl group π* orbital) of **2d** have negative energy values (−0.348 and −0.711 eV, respectively). Therefore, the electrostatic effect of the silicon atom, as well as the low energy-level of the Si–C σ* orbital, should greatly contribute to the increased electrophilicity at the silicon center in silacarboxylic acids, thereby facilitating the nucleophilic substitution.[24] These results are consistent with our hypothesis.

Accordingly, the Mitsunobu-type reaction of silacarboxylic acids with alcohols, in which the alcohol is activated in preference to silacarboxylic acids, is a judicious choice for the preparation of a variety of silacarboxyesters; achiral **2c** also undergoes smooth condensation with various alcohols (2 equiv) including methanol, ethanol and isopropanol, in the presence of DEAD (2 equiv) and PPh_3 (2 equiv),[25] to furnish silacarboxyesters tBuPhR^{1}SiCO$_2$R^2 (**8**) in moderate to good yields (Table 1, entries 1–3). Furthermore, the corresponding reaction of silacarboxylic acid (*S*)-**2b** with ethanol proceeds without any loss of enantiopurity to afford (*S*)-**8e** in high yield (90%; Table 1, entry 4).

Table 1: Mitsunobu-type reaction of silacarboxylic acids **2**.[a]

Entry	**2**	R^1	R^2OH	**8**	Yield [%][b]
1	**2c**	Ph	MeOH	**8b**	95
2	**2c**	Ph	EtOH	**8c**	95
3	**2c**	Ph	*i*PrOH	**8d**	72[c]
4	(*S*)-**2b**	*n*Bu	EtOH	(*S*)-**8e**	90

[a] Reaction conditions: R^2OH (2 equiv), DEAD (2 equiv), PPh_3 (2 equiv), THF, 0°C. [b] Yield of isolated products. [c] Silyl ester **9** was isolated in 7% yield.

In conclusion, we have described the first asymmetric synthesis of chiral silacarboxylic acids by the stereospecific carboxylation of silyllithium compounds that are derived from chiral chlorosilanes as the key step. We have also found that the silacarboxylic acids can be converted into their ester derivatives using Mitsunobu-type conditions. These results should open up the possibility for the preparation of enantiomerically enriched functional silicon compounds that may have potential utility as bioactive compounds, chiral reagents, or functional materials. Further studies on chiral silacarboxylic acids and their esters are underway.[26]

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[15] In contrast, heating of **2a** and **2b** or treatment with base caused decarbonylation to afford the corresponding silanols. A similar observation with triphenylsilyl carboxylic acid has been reported, see: A. G. Brook, H. Gilman, *J. Am. Chem. Soc.* **1955**, *77*, 2322 – 2325.
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[20] In good agreement with our observations; to the best of our knowledge the preparative methods for silacarboxyesters have been largely limited to using diazoalkane, see Ref. [15].
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[26] We have also found that the reaction of silyllithium compound **5c** with *N*, *N*- dimethyl chloroformamide in tetrahydrofuran at −78 °C provides the corresponding silacarboxamide, tBuPh$_2$SiCONMe$_2$ (**10**), albeit in low yield (20%); see the Supporting Information for details.

