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Stereoretentive Addition of *N*-*tert*-Butylsulfonyl- α -Amido Silanes to Aldehydes, Ketones, α,β -Unsaturated Esters, and Imines

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Abstract: Enantioenriched *N*-*tert*-butylsulfonyl- α -amido silanes were successfully reacted with aldehydes, ketones, imines, and α,β -unsaturated esters in the presence of a sub-stoichiometric amount of CsF (0.5 equiv) in DME at -20 °C to afford the corresponding coupling products with up to 89% enantiospecificity in a retentive manner.

The construction of C-C bonds with preservation of the optical purity of nucleophiles is a formidable challenge in organic synthesis.^[1] Although transition-metal-catalyzed stereospecific cross-coupling reactions have been actively studied in this field,^[2] much attention is still being paid to non-catalytic processes using highly reactive nucleophiles.^[3-6] Among the latter examples, stereospecific additions of secondary and tertiary alkylolithium species have been extensively studied over the past three decades.^[3] For instance, enantioenriched organolithium species, which are prepared by tin-lithium exchange from the corresponding optically active organostannanes and *n*- or *s*-BuLi,^[4] deprotonation of enantioenriched carbamate-protected derivatives with BuLi and TMEDA,^[5] or asymmetric deprotonation of achiral substrates using BuLi and (-)-sparteine as a chiral ligand,^[6] reacted with a range of electrophiles in a stereoretentive/invertive manner. However, a very low temperature (below -78 °C) was often required in order to maintain their optical purities as much as possible. Moreover, the use of highly nucleophilic BuLi attenuates the synthetic utility due to the low functional group tolerability and the need for strictly anhydrous conditions. On the

other hand, less reactive alkylboron^[7] and silane^[8] reagents were also employed for the stereospecific addition in combination with an appropriate activator. Although γ -addition of enantioenriched allylborons/silanes has already been established,^[7a-d,8a-c] stereospecific transformation of C(sp³)-B/Si into C(sp³)-C bonds is still challenging, and this has motivated us to develop a new method with a high level of enantiospecificity for versatile electrophiles under mild conditions.

Our research group already reported a stereoretentive carboxylation of α -amino silanes **1** with CO₂ in the presence of CsF in DMF solvent at -20 °C, affording the corresponding α -amino acids with up to 86% enantiospecificity (Figure 1).^[9,10] The starting enantioenriched *N*-*tert*-butylsulfonyl- α -amido silanes **1** can be synthesized either from Ellman's chiral sulfinyl imines by diastereoselective silylation^[11] followed by oxidation or from sulfonyl imines by Cu(I)-catalyzed enantioselective silylation recently developed by our group.^[10] In contrast, the use of *N*-Boc- α -amido silanes **1b** under the same conditions gave racemic compounds,^[12] suggesting that the Boc substitution enhances carbanion generation, whereas the sulfonyl group might stabilize a fluorosilicate intermediate in the stereoretentive transformation. We herein disclose the detection of a fluorosilicate species using ¹⁹F-²⁹Si 2D NMR spectroscopy in addition to other potential transformations of *N*-*tert*-butylsulfonyl- α -amido silane **1a** (R = Ph) with various electrophiles including aldehydes, ketones, α,β -unsaturated esters, and imines, affording the coupling products **2** with up to 89% enantiospecificity.

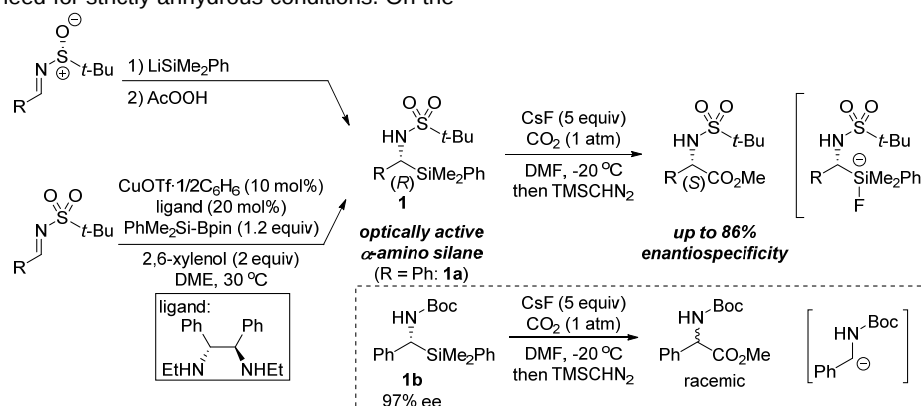


Figure 1. Carboxylation of *N*-*tert*-butylsulfonyl- α -amido silanes with CO₂.

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First, to confirm that a fluorosilicate or a carbanion is an actual nucleophilic species, ¹⁹F NMR experiments were conducted in DMF at room temperature under Ar using **1a** (R = Ph) and *N*-Boc- α -amido silane **1b** in the presence of TBAT (tetra-*n*-butylammonium triphenyldifluorosilicate: Ph₃SiF₂·NBu₄) instead of CsF as a fluoride source, because TBAT is readily soluble in DMF to keep the solution homogeneous during the analysis (Figure 2). When **1a** was subjected to ¹⁹F NMR analysis, a strong peak at -114 ppm other than TBAT (-104

ppm), PhMe_2SiF (-165 ppm), and a peak (-124 ppm) tentatively assigned as $\text{PhMe}_2\text{SiF}_2 \cdot \text{NBu}_4$, which was prepared from TBAT and PhMe_2SiF , was clearly observed.^[13] To obtain more information about this species, we then conducted a ^{19}F -detected ^{19}F - ^{29}Si gradient-enhanced heteronuclear multiple-quantum coherence (gHMQC) experiment with full ^{29}Si decoupling mode, and the results indicated that -114 ppm in ^{19}F NMR was correlated with the peak around -110 ppm in ^{29}Si NMR ($J_{\text{FSi}} = 207 \text{ Hz}$). Peaks in this region of ^{29}Si NMR generally represent silicate species,^[14] suggesting that fluorosilicate species **3** was present, probably due to the assistance of sulfonyl oxygen.

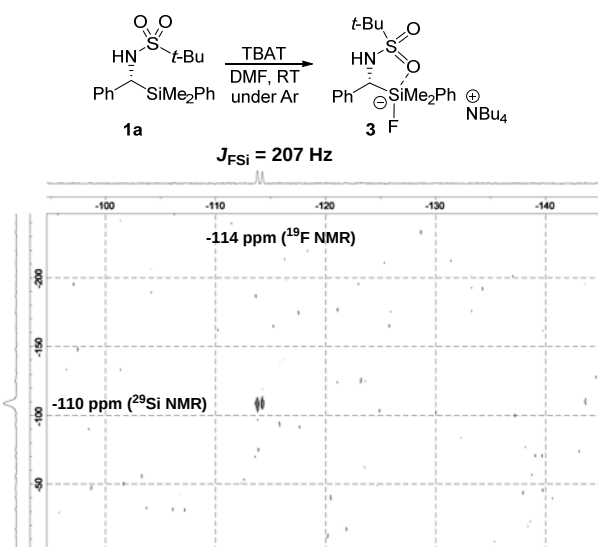


Figure 2. ^{19}F - ^{29}Si gradient-enhanced heteronuclear multiple-quantum coherence (gHMQC) experiment. (^{19}F irradiated, ^{19}F observed, and ^{29}Si decoupled mode)

^{19}F NMR experiments using *N*-Boc- α -amido silane **1b** were also conducted, and the results showed only three peaks (TBAT, PhMe_2SiF , and $\text{PhMe}_2\text{SiF}_2 \cdot \text{NBu}_4$).^[13] The presence of PhMe_2SiF and $\text{PhMe}_2\text{SiF}_2 \cdot \text{NBu}_4$ indicated that activation of the PhMe_2Si - moiety of **1b** by TBAT actually occurred. However, the formation of a carbanion from the fluorosilicate would be accelerated due to the lack of a stabilization effect of the sulfonyl group. Thereby, a reactive carbanion would be produced, followed by its racemization with loss of stereochemical information of original **1b**. Based on a comparison of the results of the experiments, the production of the fluorosilicate species **3** was thought to be involved in the stereoretentive transformation.

Given information about the fluorosilicate intermediate by NMR, nucleophilic addition of **1a** with benzaldehyde was next investigated (Table 1). When the reaction was conducted in DMF at room temperature, amino alcohol **2a** was obtained in 60% yield with almost 1:1 dr with low ee's (Entry 1). With decrease in temperature from room temperature to -20°C , the yield was slightly increased to 71% and the ee's of both diastereomers became about 60% ee (Entry 2). Further decrease of the temperature did not improve the yield and selectivities (Entry 3). When the reaction solvent was changed

from DMF to DME, the ee's increased to 79% ee (Entry 4). The ee's were further increased to around 82%/84% when the reaction was conducted using a sub-stoichiometric amount of CsF (0.5 equiv) and an excess amount of benzaldehyde (2 equiv) (Entry 5). Finally, the yield was improved to 95% by using 3 equiv of benzaldehyde (Entry 6). **1a** was completely consumed for all entries, but undesired protodesilylation proceeded, resulting in a decrease in the yield of **2a** (Entry 1: 10%; Entry 2: 2%; Entry 3: 10%; Entry 3: 11%; Entry 4: 9%; Entry 5: 5%).

Table 1. Condition Screening.

Entry	PhCHO [X]	CsF [Y]	Time [h]	Solvent	Total Yield of 2a [%] ^[a]	dr [anti/syn] ^[b]		Ee [%] ^[c] anti/syn
1 ^[d]	1.2	5	4	DMF	60	1/1		36/31
2	1.2	5	23	DMF	71	1/1		64/63
3 ^[e]	1.2	5	23	DMF	61	1.1/1		62/67
4	1.2	5	23	DME	89	1/1.3		79/79
5	2	0.5	24	DME	91	1/1.3		82/84
6	3	0.5	24	DME	95 (94)	1/1.2		83/88

[a] Yields were determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses. [b] Determined by ^1H NMR analysis. [c] Determined by chiral HPLC analysis. [d] The reaction was conducted at room temperature. [e] The reaction was conducted at -30°C .

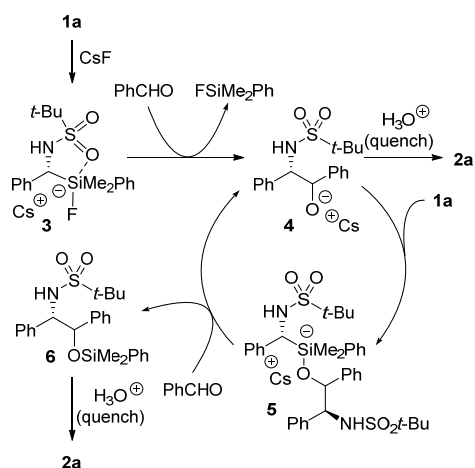


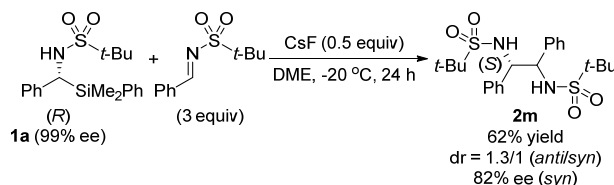
Figure 3. Proposed reaction mechanism.

Taking into account the possibility of a catalytic pathway, a reasonable reaction mechanism is proposed (Figure 3). α -Amino silane **1a** is first activated by CsF to produce fluorosilicate species **3**, which then undergoes nucleophilic addition to benzaldehyde. The generated cesium alkoxide **4** is then quenched by H_3O^+ to produce **2a** (stoichiometric pathway). On the other hand, cesium alkoxide **4** would also work as a Lewis base for activation of **1a** to produce **5**, which then

undergoes nucleophilic addition to benzaldehyde to afford **6**. The silylated alcohol **6** is then quenched by H_3O^+ to produce **2a** (catalytic pathway). Although both pathways are operative in this system, the catalytic activation seems to be effective in terms of enantiospecificity.

With optimal catalytic conditions in hand, the reaction scope and limitations were examined using **1a** as a substrate (Figure 4). Not only benzaldehyde but also aliphatic aldehydes bearing acidic α -protons were all tolerated to produce **2a-2d** with up to 89% enantiospecificity, but their diastereoselectivities were almost 1:1. The use of cinnamaldehyde as an electrophile led to selective 1,2-addition. When symmetrical ketones were employed, the coupling products **2f-2i** were obtained in moderate to good yields with almost 80% ee. The use of unsymmetrical ketones such as acetophenone and 2,2,2-trifluoroacetophenone slightly improved their diastereoselectivities, and products **2j** and **2k** were obtained with high enantiospecificity. Additionally, **1a** underwent 1,4-addition of ethyl acrylate to afford γ -amino acid **2l** in moderate yield with 76% ee.

Next, nucleophilic addition of **1a** to *N*-*tert*-butylsulfonyl imine was investigated under the optimal conditions (Scheme 1).^[15] The reaction smoothly proceeded at -20°C and the target diamine **2m** was obtained in 62% yield with a mixture of *anti* (*meso*)/*syn* (*dl*) diastereomers. The ee of (*S,S*)-*syn*-**2m** was determined to be 82%. Although the ratio of *anti*/*syn* was not satisfactory, it is noteworthy that α -amino silane reacted with imines to afford C_2 symmetric 1,2-diamines, which can be seen as backbones of various chiral ligands.



Scheme 1. Preparation of optically active 1,2-diamine.

The stereochemistry of the stereogenic center adjacent to the nitrogen atom of the product was confirmed by its derivatization (Figure 5). Amino alcohol **2a** containing *anti*/*syn* diastereomers was oxidized by Dess-Martin periodinane into a known α -amino ketone **7** in 79% yield.^[16] The absolute configuration of the stereogenic center of α -carbon was determined to be (*S*) based on comparison of its optical rotation value with the reported one.^[16] This result suggested that the present nucleophilic addition proceeded in a retentive manner similar to the case of carboxylation of **1a**.^[10]

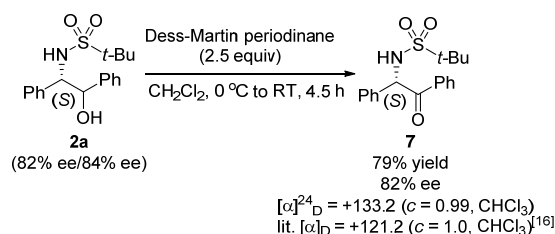


Figure 5. Determination of the absolute configuration of α -carbon of nitrogen.

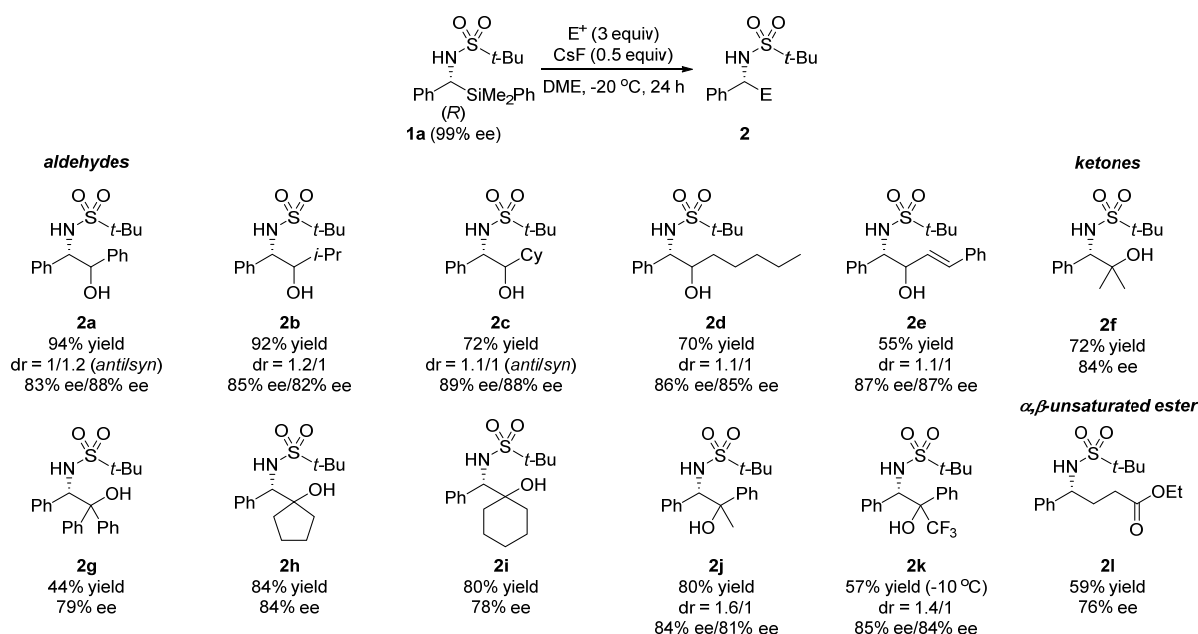


Figure 4. Substrate scope using α -amino silane **1**. Isolated yields are shown unless otherwise noted.

One of the diastereomers of **2a** (more polar product on silica gel column chromatography) derived from benzaldehyde

as well as **2c** (less polar product on silica gel column chromatography) derived from cyclohexanecarboxaldehyde

were both (S,S)-syn-diastereomers based on comparison of their NMR spectra and optical rotation values with the reported data (Figure 6).^[17] In addition, the sulfonyl group of the other diastereomer of **2a** was removed according to the reported methods,^[10,18] giving the corresponding free amino alcohol **8** in 73% yield. Its optical rotation value and NMR spectra perfectly matched those of (S,R)-anti-diastereomer.^[19]

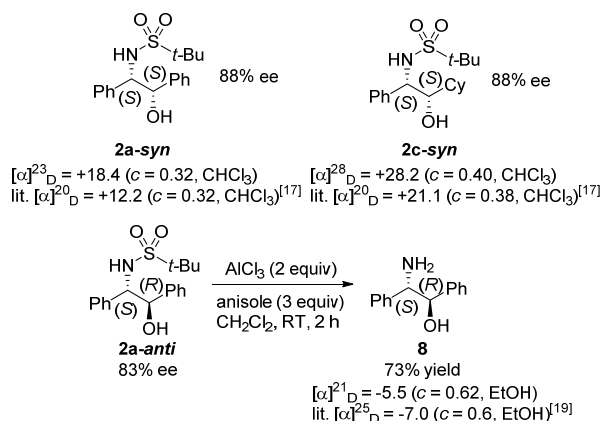


Figure 6. Determination of stereochemistry of the products.

In summary, we have developed stereoretentive addition of *N*-tert-butylsulfonyl- α -amido silanes to various electrophiles including aldehydes, ketones, α,β -unsaturated ester, and imines. Enantiospecificity was up to 89% at -20 °C in DME. Further substrate scope including nucleophiles other than **1a** is now actively underway.

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Keywords: aldehydes • ketones • silane • cesium fluoride • stereospecific

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