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Catalytic Asymmetric Rearrangement of α,α-Disubstituted α-Siloxy Aldehydes to Optically Active Acyloins Using Axially Chiral Organoaluminum Lewis Acids

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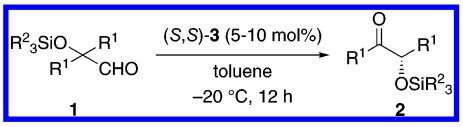
The skeletal rearrangements involving 1,2-carbon-to-carbon migration are fundamental yet powerful methods for the structural reorganization of organic molecules through the consecutive or concurrent cleavage and formation of carbon−carbon bonds,[1] often making it feasible to construct otherwise inaccessible molecular frameworks. However, precise control of the stereochemical outcome together with the migratory aptitude is not a trivial task mainly because of the proneness to generate an intermediary carbocation under the conventional conditions. Thus, research for the elaboration of stereoselective variants had long been circumvented. The delivery of effective Lewis acids to this field resulted in an important progress, enabling the *stereospecific* reaction using chiral substrates, which generally establishes complete chirality transfer with either stoichiometric or catalytic amount of an appropriate promoter.[2] Nevertheless, such endeavors are still very limited, and in turn, examples of success in the *enantioselective* 1,2-rearrangement of achiral substrates by the use of chiral activator, especially in a catalytic quantity, have been extremely rare despite its conceptual and practical significance.[3] In conjunction with our recent studies on the organoaluminum-promoted selective rearrangement of aminocarbonyl compounds,[4] we here report our own approach toward this subject, that is, the development of skeletal rearrangement of α,α-dialkyl-α-siloxy aldehydes **1**, which can be efficiently catalyzed by newly designed chiral organoaluminum Lewis acid **3** with high enantioselectivity, thereby offering a facile access to various optically active acyloins (Scheme 1).[5]

On the basis of our preliminary studies on the search for suitable chiral Lewis acid catalysts with α,α-dibenzyl-α-trimethylsiloxy aldehyde (**1a**, R^2 = Me) as a representative substrate,[6] we designed a new axially chiral organoaluminum Lewis acid **3** that possesses the chiral environment created by the 2-[3,5-bis(trifluoromethyl)-phenyl]-substituted naphthyl moiety being extended over the coordination site of the aluminum, possibly enabling rigorous stereocontrol.

The requisite ligand **4** can be synthesized from (*S*)-BINOL in a seven-step sequence.[7] Interestingly, the molecular structure of **4** visualized by the single-crystal X-ray diffraction analysis adopted homochiral (*S*,*S*) configuration (Scheme 1, cylinder model),[7,8] and refluxing a solution of **4** in toluene for 24 h showed no conformational interconversion between (*S*,*S*) and (*S*,*R*) isomers. Thus, treatment of (*S*,*S*)-**4** (1.1 equiv) with Me_3Al in toluene at room temperature for 30 min generated in situ the stereochemically defined methylaluminum catalyst (*S*,*S*)-**3** (10 mol %),[9] and subsequent reaction with **1a** (R^2 = Me) at −20 °C for 12 h resulted in clean formation of the desired α-siloxy ketone **2a** (R^2 = Me) in 96% yield with 77% ee (entry 1 in Table 1). This promising result prompted us to evaluate the effect of the trialkylsilyl group on the stereoselectivity, and α-triethylsiloxy linkage in **1a** was found to be optimal, leading to the quantitative production of the rearranged **2a** (R^2 = Et) with 87% ee under similar conditions (entry 2). Notably, the catalyst loading can be reduced to 5 mol % without significant loss of reactivity and selectivity (entry 4).

With the optimized conditions in hand, we conducted the experiments to probe the scope of this new catalytic asymmetric 1,2-rearrangement, and the selected examples are included in Table 1.[10] Generally, the reaction proceeded smoothly at −20 °C under the influence of 5 mol % of (*S*,*S*)-**3**. A series of α-siloxy aldehydes bearing α-benzylic substituents of different electronic properties were tolerated (entries 5−8). The substrates having allylic α-sub-

Table 1. Catalytic Asymmetric Rearrangement of α,α-Dialkyl-α-siloxy Aldehydes **1** with (*S*,*S*)-**3**[a]



1 2

entry	R^1	$R^2{}_3$	% yield[b]	% ee[c]	product
1	$PhCH_2$ (**1a**)	Me_3	96	77	**2a**
2	$PhCH_2$ (**1a**)	Et_3	99	87	**2a**
3	$PhCH_2$ (**1a**)	*t*-$BuMe_2$	99	80	**2a**
4	$PhCH_2$ (**1a**)	Et_3	96	87	**2a**
5	*p*-MeO−$C_6H_4CH_2$ (**1b**)	Et_3	98	85	**2b**
6	*p*-F−$C_6H_4CH_2$ (**1c**)	Et_3	97	90	**2c**
7	*p*-Cl−$C_6H_4CH_2$ (**1d**)	Et_3	94	86	**2d**
8	2-NaphCH_2 (**1e**)	Et_3	95	85	**2e**
9	*trans*-PhCH=$CHCH_2$ (**1f**)	Et_3	81	83	**2f**
10	$(CH_3)_2C$=$CHCH_2$ (**1g**)	Et_3	84	80	**2g**
11	$(CH_3)_2CHCH_2$ (**1h**)	Et_3	94	74	**2h**
12	*c*-Hex (**1i**)	Et_3	97	74	**2i**

[a] The reaction was carried out with either 10 mol % (entries 1−3) or 5 mol % (entries 4−12) of (*S*,*S*)-**3** in toluene at −20 °C for 12 h. [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis. The absolute configuration of **2a** was determined to be *S* by comparison of the optical rotation with a literature value after desilylation.[4]

Scheme 1

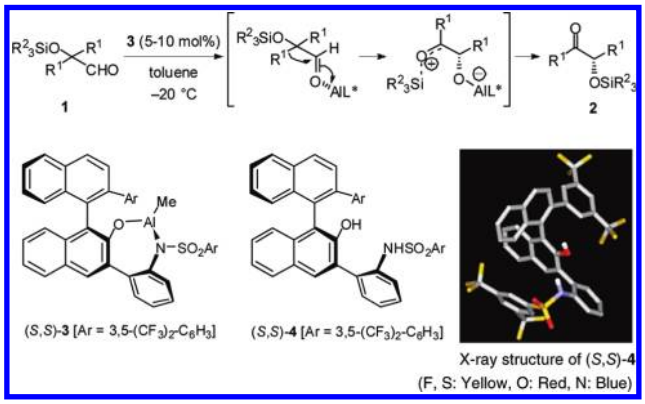


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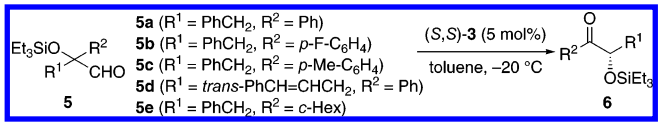
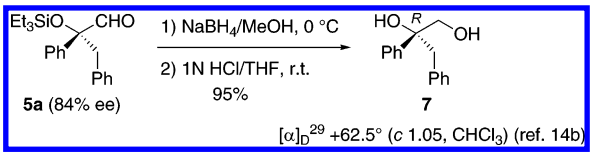
Table 2. Kinetic Resolution of Differently α,α-Disubstituted α-Siloxy Aldehydes **5**[a]



entry	**5**	time (h)	% yield of **6**[b]	% ee[c,d] (config)	recovery of **5** (%)[b]	% ee[c,e] (config)	*s*
1	**5a**	12	49 (**6a**)	86 (*S*)	51	84 (*R*)	39.5
2	**5a**	15	55 (**6a**)	79 (*S*)	45	92 (*R*)	22.7
3	**5b**	11	49 (**6b**)	86	51	85	44.2
4	**5c**	12	51 (**6c**)	85	49	83	22.8
5	**5d**	3	57 (**6d**)	63	43	90	15.6
6	**5e**	0.5	55 (**6e**)	77	44	88	17.5

[a] The reaction was conducted with 5 mol % of (*S*,*S*)-**3** in toluene at −20 °C for the given reaction time. [b] Isolated yield. The ratio of **6** to the product through the migration of R^2 was >20:1. [c] Determined by HPLC analysis. [d] The absolute configuration was determined by comparison of the optical rotation with a reported value after desilylation.[16] [e] For assignment of the absolute configuration, see Scheme 2.

Scheme 2



stituents also underwent highly enantioselective rearrangement, featuring the advantage of this method to construct enantiomerically enriched acyloins not readily accessible by the previously known methodologies (entries 9 and 10).[5] It should be emphasized that extremely facile migration of a simple alkyl group was realized with good enantioselectivity (entries 11 and 12).

To further expand the scope of the present system, we investigated the rearrangement of racemic, differently α,α-disubstituted α-siloxy aldehydes **5**, which uncovered the impressive level of kinetic resolution (Table 2),[11] making it feasible not only to broaden the applicability but also to prepare optically active tertiary α-hydroxy aldehydes.[12] When **5a** was treated with 5 mol % of (*S*,*S*)-**3** in toluene at −20 °C for 12 h, α-hydroxy ketone **6a** was obtained almost exclusively in 49% yield with 86% ee (*S*), and **5a** was recovered in 51% yield with 84% ee (entry 1, selectivity factor: $s = 39.5$).[13] Performing the reaction for 15 h under otherwise similar conditions enabled the isolation of **5a** in 45% yield with 92% ee (entry 2). The absolute configuration of the recovered **5a** was determined to be *R* by conversion to the diol **7** (Scheme 2), a known compound whose asymmetric synthesis was dependent upon enzymatic resolution.[14] This assignment confirms the highly stereospecific rearrangement of (*S*)-**5a** to (*S*)-**6a**.[15] Other examples listed in Table 2 showed the migratory aptitude and stereoselectivity corresponding to the combination of the two different α-substituents in **5**. These results demonstrate potential synthetic utility of our approach and also suggest that the origin of the asymmetric induction lies on the ability of **3** to discriminate the α-stereogenic center of the substrates.

In summary, we have invented an asymmetric rearrangement of α,α-dialkyl-α-siloxy aldehydes to α-siloxy ketones efficiently catalyzed by the newly designed, axially chiral organoaluminum Lewis acid under mild conditions, and a kinetic resolution of racemic, differently α,α-disubstituted substrates has also been achieved. This is the first example of catalytic, highly enantioselective 1,2-rearrangement of α-alkoxycarbonyl compounds and provides a unique tool for the synthesis of various acyloins and tertiary α-hydroxy aldehydes of high enantiomeric purities. Further intensive studies on the application of this approach are currently underway in our laboratory.

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Supporting Information Available: Representative experimental procedures and spectroscopic characterization of new compounds (PDF); the crystallographic data for (*S*,*S*)-**4** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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