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Skeletal Rearrangement

Complete Switch of Migratory Aptitude in Aluminum-Catalyzed 1,2-Rearrangement of Differently α,α-Disubstituted α-Siloxy Aldehydes**

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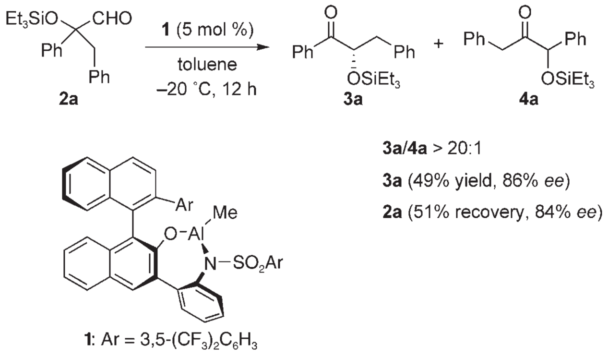
Skeletal rearrangements involving 1,2-carbon-to-carbon migration are powerful methods for the structural reorganization of organic molecules,[1] and they often make it feasible to construct otherwise hard-to-access molecular frameworks. Unsymmetrical substrates, however, generally give a mixture of structural isomers, which constitutes a major drawback of the 1,2-rearrangement and debases its synthetic utility. Thus, research into the regioselective 1,2-rearrangement to afford a single product is of practical importance. A common approach to this subject is the design of substrates based on the relative migratory aptitudes of the substituents[2] and/or conformational effects,[3] which often establishes selective transformation leading to the most favorable isomers. Nevertheless, this strategy requires the preparatory installation of all structural features that will drive the rearrangement in the desired direction, and, in principle, the obtainable products are restricted to just one. In contrast, intentional control of the migratory tendency for the selective synthesis of any isomer from one substrate by switching the migrating group is challenging and attractive. Even now, successful examples to address this issue are very limited.[4]



3a/**4a** > 20:1
3a (49% yield, 86% *ee*)
2a (51% recovery, 84% *ee*)

Scheme 1. 1,2-Rearrangement of the differently α,α-disubstituted α-siloxy aldehyde **2a**.

As part of our research on aluminum-mediated selective 1,2-migrations, we recently developed an enantioselective 1,2-rearrangement of α,α-disubstituted α-siloxy aldehydes by using the chiral aluminum Lewis acid **1**,[5] in which a kinetic resolution of racemic, differently α,α-disubstituted α-siloxy aldehydes was also achieved. When α-siloxy aldehyde **2a** was treated with **1** in toluene at −20 °C for 12 h, siloxy ketone **3a** was obtained almost exclusively in 49 % yield with 86 % *ee*, along with recovered **2a** (51 %, 84 % *ee*; Scheme 1). Although the observed predominant formation of **3a** is explicable by assuming selective migration of the benzyl group over the phenyl group (with subsequent transfer of the silyl group), such an interpretation is inconsistent with common understanding because the prominent migratory ability of the phenyl group has been well-documented in pinacol and Wagner–Meerwein rearrangements. This contradiction prompted us to pursue further research in a new direction in order to figure out the crucial element governing the unique regioselectivity of this reaction, which would enable the selective preparation of any isomer at will. Herein, we detail our discovery of an unprecedented regiodivergent 1,2-rearrangement of differently α,α-disubstituted α-siloxy aldehydes.

Our initial investigation was focused on verification of the effect of the Lewis acid catalyst on the regioselectivity in the reaction of **2a**. Since the previously reported aluminum Lewis acid **1** has the two characteristic features of steric hindrance and relatively weak Lewis acidity, we first examined the impact of the bulkiness of catalyst, and the rearrangement of **2a** was thus conducted with a series of sterically hindered aluminum Lewis acids[6] (Table 1). Interestingly, the use of ATPH[7] as a catalyst was found to provide an equimolar mixture of the two isomers, **3a** and **4a** (Table 1, entry 1). Whereas a similar product distribution was retained in the reaction with MABR,[8] **3a** was obtained preferentially, with a **3a**/**4a** ratio of 5:1, when the structurally similar but less Lewis acidic MAD[9,10] was employed (Table 1, entries 2 and 3). These results, particularly the distinct difference in the regioselectivity between the reactions with MABR and MAD, imply that the selectivity is influenced by the Lewis acidity of the catalyst rather than its steric size. Enhancement of the Lewis acidity might thus lead to an increase in the proportion of **4a** in the rearranged products.

We next performed the reactions of **2a** with other catalysts to elucidate the relationship between the regiose-

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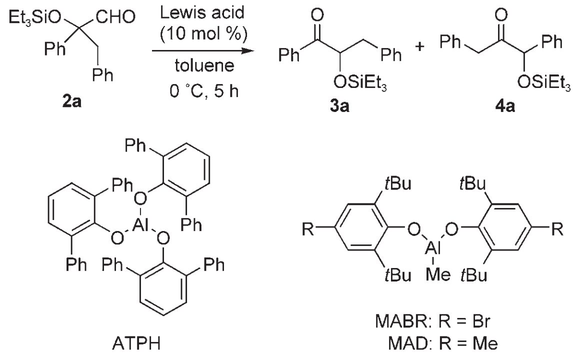
Table 1: 1,2-Rearrangement of α-siloxy aldehyde **2a** with sterically hindered aluminum Lewis acids.[a]

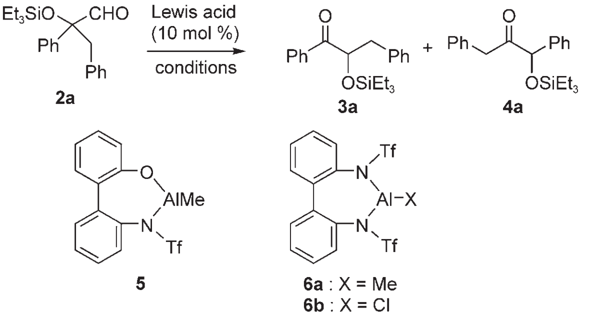


Entry	Lewis acid	Yield [%][b]	**3a**/**4a**[c]
1	ATPH	29	1:1
2	MABR	45	1:1
3	MAD	35	5:1

[a] The reaction was carried out with 10 mol% of the Lewis acid under the given reaction conditions. [b] Product isolated as a mixture of **3a** and **4a**. [c] Determined by ^{1}H NMR analysis.

lectivity and the Lewis acidity (Table 2). Initially, we found that one of the most conventional aluminum Lewis acids, Me$_2$AlCl, promoted the rearrangement of **2a** to **3a** with complete selectivity (Table 2, entry 1). Biphenyl-based aluminum Lewis acids, such as **5**[11] and **6**,[12] were then chosen for further examinations because their Lewis acidities could be readily regulated by an appropriate combination of the heteroatoms bound to aluminum. The attempted reaction of **2a** with **5** preferentially provided **3a** (with a 5:1 ratio of **3a**/**4a**), and switching of the catalyst to the comparatively strong Lewis acid **6a** reduced the regioselectivity (Table 2, entries 2 and 3). Moreover, the product distribution was reversed in the reaction under the influence of **6b**, which has even higher Lewis acidity (Table 2, entry 4); this result supported the hypothesis that a stronger Lewis acid might lead to an increase in the proportion of **4a** in this rearrangement. Encouraged by these interesting results, we subsequently tuned the reaction parameters to enhance the preference toward the formation of **4a**. To our delight, use of CH$_2$Cl$_2$ instead of toluene as a solvent led to an improvement in the selectivity (Table 2, entries 5 and 4), and **4a** was eventually isolated as the only product by lowering the reaction temperature to −20 °C (Table 2, entry 6).

Table 2: Reaction of **2a** with four Lewis acids.[a]

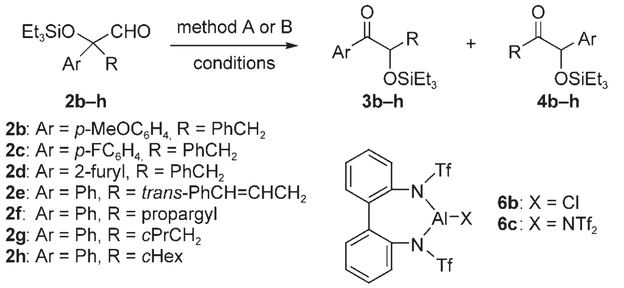


Entry	Lewis acid	Solvent	T [°C]	t [h]	Yield [%][b]	**3a**/**4a**[c]
1	Me$_2$AlCl	toluene	0	24	91	> 20:1
2	**5**	toluene	0	24	71	5:1
3	**6a**	toluene	0	24	99	3:1
4	**6b**	toluene	0	24	99	1:1.5
5	**6b**	CH$_2$Cl$_2$	0	12	99	1:4
6	**6b**	CH$_2$Cl$_2$	−20	12	99	< 1:20

[a] The reaction was carried out with 10 mol% of the Lewis acid under the given reaction conditions. [b] Product isolated as a mixture of **3a** and **4a**. [c] Determined by ^{1}H NMR analysis.

We next evaluated the substrate scope of the regiodivergent 1,2-rearrangement of α-siloxy aldehydes with different Al catalyst/solvent systems (Table 3). By a judicious choice of method, reversals of selectivity were observed in the reactions of α-triethylsiloxy aldehydes bearing benzyl and various aryl substituents (Table 3, entries 1–7). For these substrates, the catalytic Me$_2$AlCl system in toluene (method A) was uniformly effective, and α-siloxy ketones **3** were obtained with good to excellent selectivities (Table 3, entries 1, 3, and 6). Although the rearrangement of **2c** with an electron-deficient aryl group proceeded sluggishly and exhibited poor regioselectivity under the influence of **6b**, almost quantitative yield and high selectivity were achieved with **6c** at a lower

Table 3: 1,2-Rearrangement of α-siloxy aldehydes **2** with several aluminum Lewis acid/solvent systems.



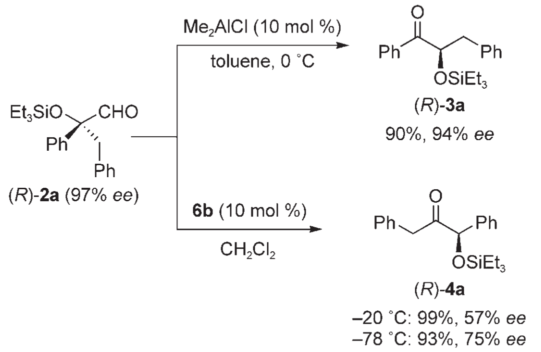
2b: Ar = p-MeOC$_6$H$_4$, R = PhCH$_2$
2c: Ar = p-FC$_6$H$_4$, R = PhCH$_2$
2d: Ar = 2-furyl, R = PhCH$_2$
2e: Ar = Ph, R = *trans*-PhCH=CHCH$_2$
2f: Ar = Ph, R = propargyl
2g: Ar = Ph, R = cPrCH$_2$
2h: Ar = Ph, R = cHex

Entry	Substrate	Method[a]	T [°C]	t [h]	Yield [%][b]	**3**/**4**[c]
1	**2b**	A	0	24	91	10:1
2	**2b**	B-1	−20	12	99	< 1:20
3	**2c**	A	0	24	93	> 20:1
4	**2c**	B-1	−20	12	64	1:5
5	**2c**	B-2	−40	24	98	< 1:20
6	**2d**	A	0	24	61	> 20:1
7	**2d**	B-1	−20	24	71	< 1:20
8	**2e**	A	0	24	99	> 20:1
9	**2e**	B-1	−20	24	99	1:3
10	**2e**	B-2	−50	48	63	< 1:20
11	**2f**	A	RT	48	60	> 20:1
12	**2f**	B-1	−20	48	76	< 1:20
13	**2g**	A	0	24	97	11:1
14[d]	**2g**	B-1	−20	12	99	< 1:20
15	**2h**	A	RT	24	81	3:1
16	**2h**	B-1	−20	24	73	< 1:20

[a] Method A: 10 mol% Me$_2$AlCl in toluene. Method B-1: 10 mol% **6b** in CH$_2$Cl$_2$. Method B-2: 10 mol% **6c** in CH$_2$Cl$_2$. [b] Product isolated as a mixture of **3** and **4**. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] The rearranged product **4f** easily isomerized to the corresponding allenyl ketone.[14].

temperature (Table 3, entries 4 and 5). Subsequently, phenyl- and various alkyl-substituted substrates, **2e**–**h**, were examined (Table 3, entries 8–16). Although method B-2 proved to be superior for the selective formation of siloxy ketones **4**, the complicated procedure for the preparation of **6c**[13] led us to employ it only when unsatisfactory results were obtained with **6b**. For instance, the selectivity in the transformation of **2e** with phenyl and allylic substituents to the corresponding siloxy ketone **4** was greatly improved by changing the method from B-1 to B-2 (Table 3, entries 9 and 10). On the other hand, excellent regiodivergent rearrangements were feasible with phenyl- and propargyl- or phenyl- and cyclopropylmethyl-substituted substrates (**2f** and **2g**, respectively), for which the use of method B-1 was sufficient for the exclusive production of **4** (Table 3, entries 11–14). Furthermore, the phenyl- and cyclohexyl-substituted aldehyde **2h** was also tolerated (Table 3, entries 15 and 16).

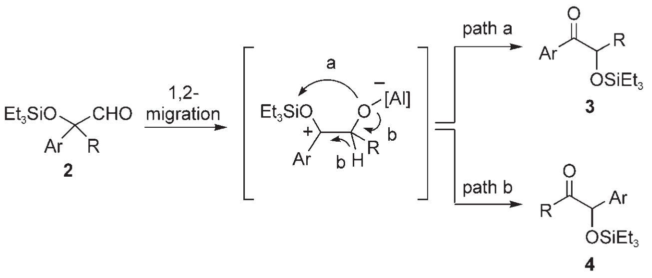
The reactions of optically active substrate (*R*)-**2a** were also examined. When (*R*)-**2a** (97% *ee*) was treated with Me_2AlCl (10 mol%) in toluene at 0°C for 24 h, the rearranged product **3a** was isolated in 90% yield with 94% *ee* (Scheme 2). By contrast, unfortunately, the reaction with catalyst **6b** was concomitant with a significant decrease in the *ee* value, probably due to the intervention of the two competing transition states, and this resulted in a maximum enantioselectivity of 75%.



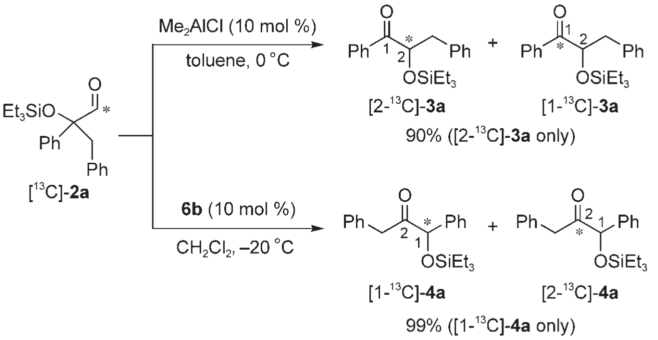
Scheme 2. 1,2-Rearrangement of optically active α-siloxy aldehyde (*R*)-**2a**.

Next, we turned our attention to the reaction pathway. 1,2-Rearrangement of α-siloxy aldehyde **2** to α-siloxy ketones **3** or **4** would be initiated by activation of the aldehyde through coordination of the Lewis acid, which promotes the nucleophilic migration of the α substituent. After this initial migration, two mechanistic rationales are conceivable for quenching the remaining cation; one is intra- or intermolecular transfer of the silyl group (path a) and the other is a 1,2-hydride migration (path b; Scheme 3).

In order to clarify whether silyl-group transfer or 1,2-hydride migration is involved in quenching the zwitterionic intermediate, the reactions were performed with the ^{13}C-labeled (C*) substrate [^{13}C]-**2a** (Scheme 4). When aldehyde [^{13}C]-**2a** was treated with Me_2AlCl (10 mol%) in toluene at 0°C (optimized method A), siloxy ketone [2-^{13}C]-**3a** was obtained as the only product, and the isomer [1-^{13}C]-**3a** was not detected by either ^1H or ^{13}C NMR spectroscopy. Furthermore, upon treatment with **6b** in CH_2Cl_2 at −20°C (method B-1), [^{13}C]-**2a** underwent selective transformation into product [1-^{13}C]-**4a**, in which the ^{13}C label was incorporated as the carbon atom bearing the ethereal oxygen atom. If a 1,2-hydride shift had occurred, isomers [1-^{13}C]-**3a** and [2-^{13}C]-**4a** incorporating the ^{13}C label as the carbonyl carbon atom would have been produced. Thus, these results unequivocally confirmed that the rearrangement exclusively proceeded through the silyl-transfer process and that the regiodivergent synthesis of siloxy ketones **3** and **4** essentially stemmed from the switch of the migrating group.



Scheme 3. The two possible reaction pathways.



Scheme 4. 1,2-Rearrangement of the ^{13}C-labeled substrate [^{13}C]-**2a**.

In summary, a complete switch of migratory aptitude in the 1,2-rearrangement of differently α,α-disubstituted α-siloxy aldehydes has been realized by using different Al catalysts and conditions, and we have successfully demonstrated that the methods to rigorously control the group migration could be applied to various substrates. These investigations should pave the way for the development of a new protocol for the selective preparation of any structural isomer from one substrate by switching the migratory tendency in the skeletal rearrangement. Further studies are underway to gain a deep insight into the mechanism of these unprecedented regiodivergent rearrangements.

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[13] **6c** was prepared from Me_2AlCl, $AgNTf_2$, and 2,2′-bis(trifluoromethanesulfonylamino)-1,1′-biphenyl. For details, see the Supporting Information.

[14] While the reaction of **2f** by using method B-1 resulted in the desired selective rearrangement, the product immediately tautomerized to the allenyl ketone.