DOI: 10.1002/ejoc.200500845

Crucial Role of the Conjugate Base for Silyl Lewis Acid Induced Mukaiyama Aldol Reactions

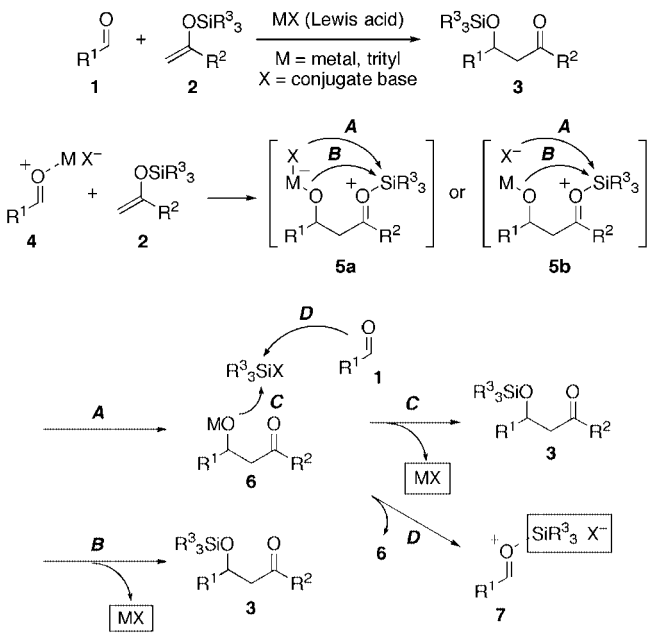
Yukihiro Hiraiwa,[a] Kazuaki Ishihara,[b] and Hisashi Yamamoto*[a]

Keywords: Mukaiyama aldol reaction / Reaction mechanism / Silyl Lewis acid / Conjugate base

The silyl Lewis acid induced Mukaiyama aldol reaction proceeds through each catalytic cycle under the influence of their conjugate bases; there is an especially significant difference between the low nucleophilic conjugate bases, $^{-}NTf_2$ and $^{-}CTf_3$, and the relatively high nucleophilic ^{-}OTf.

Introduction

Mechanistic investigations for Lewis acid induced Mukaiyama aldol reactions have been demonstrated over the last decade.[1–4] The possible and proposed pathways for the Lewis acid catalyzed Mukaiyama aldol reaction of silyl enol ether **2** with the aldehyde **1** are shown in Scheme 1. The reaction of the activated aldehyde **4** and the silyl enol ether **2** generates the silyloxycarbenium intermediate **5a** or **5b**.[5] The intermolecular transfer of the silyl group to conjugate base X produces the metal aldolate **6** and the silyl Lewis acid ($R^3{}_3SiX$) derived from silyl enol ether (path ***A***). This reaction pathway may account for the relatively high nucleophilicity of ligand X. When the metathesis between **6** and $R^3{}_3SiX$ is faster than the coordination of **1** to $R^3{}_3SiX$, the catalyst MX regenerates to give the silyl aldolate **3** (path ***C***). On the other hand, the silyl Lewis acid catalysis eventuates from the slow metathesis (path ***D***). Meanwhile, at the stage of intermediate **5a** or **5b**, the silyl group can be captured by the carbonyl substrate (path ***B***). In this case, the Lewis acid catalyst regenerates directly. Among these possible reaction mechanisms, however, the common conclusions in notable mechanistic studies can be summarized as follows: (1) the generation of the silyl Lewis acid derived from silyl enol ether, and (2) one of the real catalysts is derived from this powerful silyl Lewis acid generated in situ rather than from the Lewis acid catalyst.[2–4]



Scheme 1.

Recently, we demonstrated that Me_3SiNTf_2[6–9] shows a strong catalytic activity for the Mukaiyama aldol reaction and the Sakurai-Hosomi allylation reaction.[10] The conjugate base, $^{-}NTf_2$, is well recognized as a strong electron-withdrawing and weakly coordinating counteranion, that is a ligand of low nucleophilicity.[11] The counteranion of tris(triflyl)methane ($^{-}CTf_3$) is also known as a weakly coordinating counteranion, and the corresponding Brønsted acid ($HCTf_3$) was reported to be one of the strongest acids in the gas phase.[12–14] To date, the mechanistic studies on Lewis acid induced Mukaiyama aldol reactions reported

[a] The Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637, USA
Fax: +1-773-702-0805
E-mail: yamamoto@uchicago.edu
[b] Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya, 464-8603, Japan
Fax: +81-52-789-3222
E-mail: ishihara@cc.nagoya-u.ac.jp

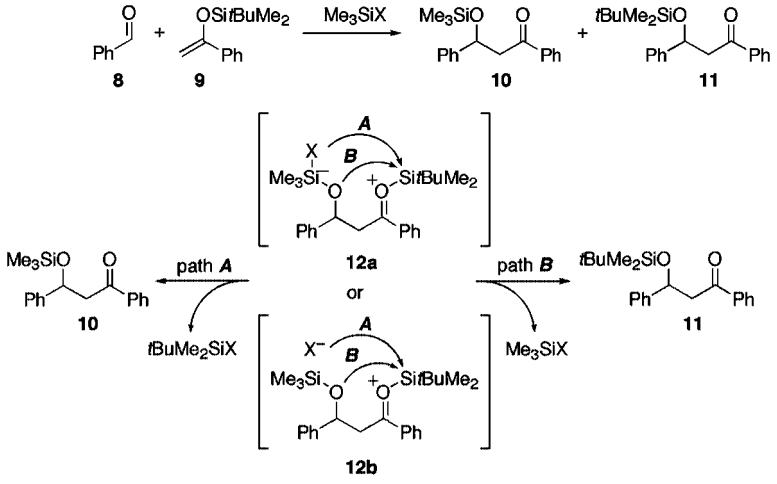
have lacked any focus on the role of conjugate base on the Lewis acid catalyst. Herein, we describe the diversity of the reaction mechanism, which is dependent on the conjugate base in silyl Lewis acid induced Mukaiyama aldol reactions.[15]

Results and Discussion

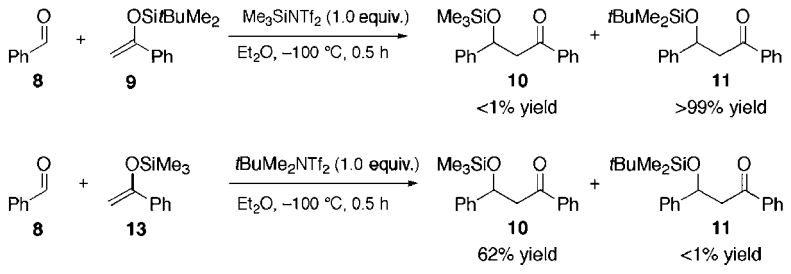
Initially, we considered two extreme mechanisms for silyl Lewis acid induced Mukaiyama aldol reactions.[4] These are illustrated in Scheme 2, where the Mukaiyama aldol reaction of tBuMe$_2$Si-enol ether **9** with benzaldehyde (**8**) is an example and where a trimethylsilyl Lewis acid (Me$_3$SiX) is employed as the catalyst. In the first stage of the catalytic process, the addition of the silyl enol ether **9** to the aldehyde **8** should generate a siloxocarbenium ion intermediate **12a** or **12b**. In path ***A***, tBuMe$_2$SiX is released from the intermediate **12a** or **12b** to give the Me$_3$Si aldolate **10** by intramolecular transfer of the counteranion X$^-$. Thus, tBuMe$_2$SiX emerges as the catalyst for the next reaction path. On the other hand, in path ***B***, the Me$_3$SiX is released into the reaction medium to provide the tBuMe$_2$Si aldolate **11** by intramolecular transfer of tBuMe$_2$Si$^+$. Therefore, Me$_3$SiX plays a role as a catalyst in path ***B***. We assumed that this reaction mechanism can be expected from the ratio of the resulting silyl aldolates **10** and **11** when the reaction is conducted in the presence of 1.0 equiv. of Me$_3$SiX.

Mechanistic Study on the R$_3$SiNTf$_2$-Induced Mukaiyama Aldol Reaction

Firstly, the mechanistic details of the Me$_3$SiNTf$_2$-induced Mukaiyama aldol reaction were investigated. To clarify whether the transformation from **12a** or **12b** to a silyl aldolate occurs through X$^-$ (path ***A***) or R$_3$Si$^+$ transfer (path ***B***), the aldol reaction of tBuMe$_2$Si enol ether **9** with benzaldehyde (**8**) was carried out in the presence of 1.0 equiv. Me$_3$SiNTf$_2$ (Scheme 3). To control the strong Lewis acidity of Me$_3$SiNTf$_2$, Et$_2$O was used as a solvent for the experiments.[10] Regardless of the addition of substrates and Me$_3$SiNTf$_2$, only the tBuMe$_2$Si aldolate **11** was produced. In contrast, the reaction of Me$_3$Si enol ether **13** with **8** in the presence of 1.0 equiv. of tBuMe$_2$SiNTf$_2$ gave the exclusive formation of Me$_3$Si aldolate **10** in moderate yield. Furthermore, neither the silyl group of tBuMe$_2$Si aldolate **11** and Me$_3$Si aldolate **10** nor that of silyl enol ethers **9** and **13** was exchanged under similar reaction conditions.[16] These experimental results would exclude the silyl catalysis path ***A*** derived from silyl enol ether, and indicate the possibility of path ***B***.

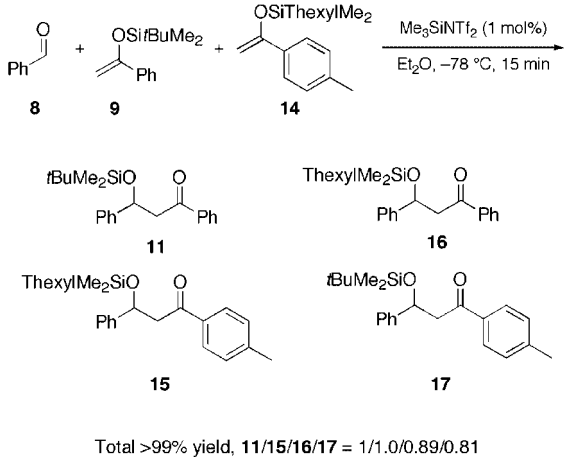


Scheme 2.



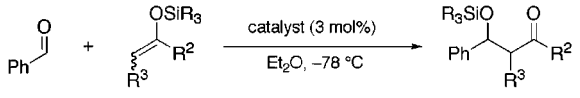
Scheme 3.

However, the double-label crossover experiment, in a manner similar to that described by Carreira and Denmark,[2,3] demonstrated the feasibility of path ***A*** (Scheme 4). Two silyl enol ethers of similar steric and electronic demands (**9** and **14**) were prepared and combined with benzaldehyde (**8**) in the presence of 1 mol-% of Me_3SiNTf_2. The reaction was complete at –78 °C within 15 min, and the product composition was determined by GC analysis. A mixture of scrambled silyl aldolates was isolated in a ratio of 1:1.0:0.89:0.81 (**11/15/16/17**). Control experiments showed that neither the starting silyl enol ethers **9** and **14** nor the silyl aldolates **11** and **15** were exchanged under-



Scheme 4.

Table 1. *syn*/*anti* Selectivity in the Mukaiyama aldol reaction.



Entry	Silyl Enol Ether	Catalyst[c]	*syn*/*anti*[d]
1	OSiMe3	Me_3SiNTf_2	60/40
2	**18**	$tBuMe_2SiNTf_2$	62/38
3	OSi*t*BuMe2	Me_3SiNTf_2	52/48
4	**19**	$tBuMe_2SiNTf_2$	51/49
5	OSiMe3 Ph	Me_3SiNTf_2	61/39
6	**20**[a]	$tBuMe_2SiNTf_2$	58/42
7	OSi*t*BuMe2 Ph	Me_3SiNTf_2	87/13
8	**21**[b]	$tBuMe_2SiNTf_2$	87/13

[a] (*E*)/(*Z*) = 1:99, determined by ^{1}H NMR spectroscopy. [b] (*E*)/(*Z*) = 4:96, determined by ^{1}H NMR spectroscopy. [c] Prepared in situ by the treatment of $AgNTf_2$ with the corresponding silyl chloride in Et_2O at room temp. for 0.5 h. [d] Determined by ^{1}H NMR spectroscopy.

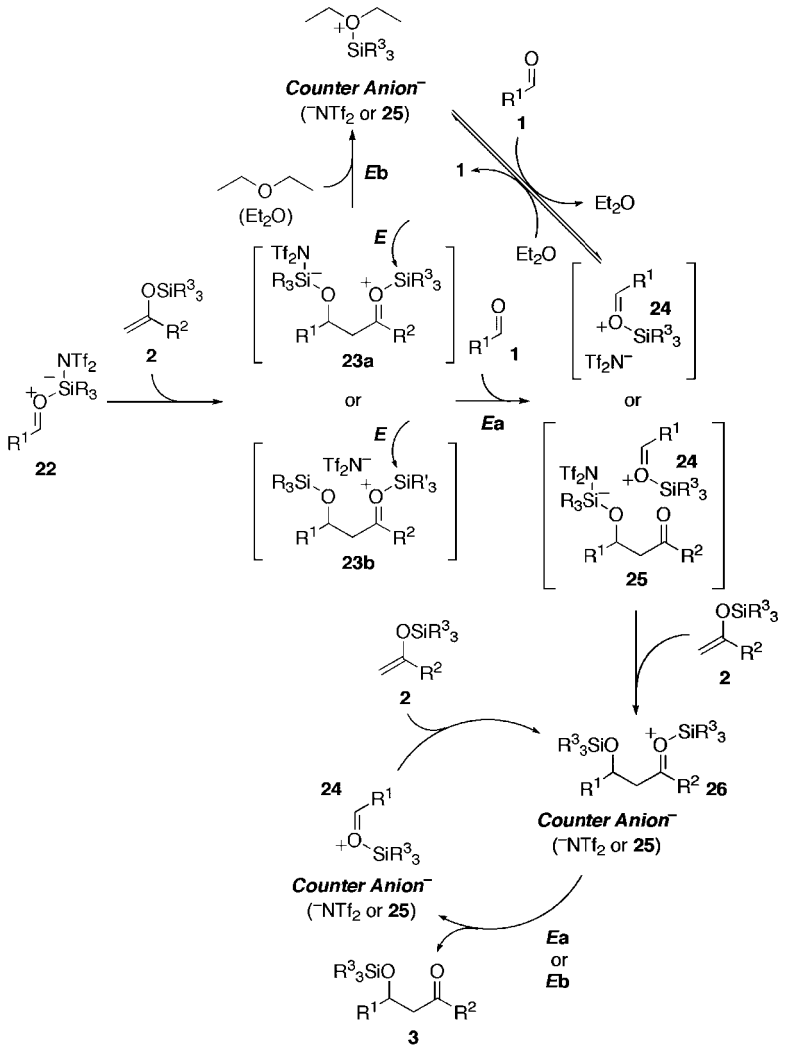
similar conditions. These facts unambiguously preclude path ***B*** and suggest the silyl group transfer between intermediates.

While the intermolecular silyl group transfer is in conflict with the afore-mentioned results for the control experiments in Scheme 3, the investigations of the *syn*/*anti* selectivities in R_3SiNTf_2-induced aldol reactions advocates the exchange of the silyl group in the reaction course. The reactions of (*E*)- and (*Z*)-silyl enol ethers **18**–**21** with aldehyde **8** were conducted in the presence of 3 mol-% of R_3SiNTf_2 (Table 1). Similar *syn*/*anti* ratios of the products were obtained, which are independent of the size of the trialkylsilyl group of the catalyst. In contrast, the diastereoselectivities correlate to the size of the silyl groups of the silyl enol ether. These experimental data indicate that the catalysis is initiated by the silyl group of silyl enol ether.

Plausible Mechanism for the R_3SiNTf_2-Induced Mukaiyama Aldol Reaction

In order to explain the results of the control experiments (Scheme 3) and the crossover experiment (Scheme 4), it was imperative to postulate another mechanism for the R_3SiNTf_2-induced Mukaiyama aldol reaction, since neither path ***A*** nor ***B*** could account for the results. With the low nucleophilicity of $^-NTf_2$ in mind, we proposed the novel reaction mechanism ***E*** for the R_3SiNTf_2-induced Mukaiyama aldol reaction (Scheme 5). In path ***E*****a**, the direct interception of the silyl group (–SiR^3_3) in intermediate **23a** or **23b** by aldehyde **1** would provide the silyloxycarbenium cation intermediate **24**. Nucleophilic attack of silyl enol ether **2** on **24** would generate the other silyloxycarbenium cation intermediate **26**, and the reaction would proceed in the same manner. Additionally, we considered the role of Et_2O for the alternative reaction mechanism (path ***E*****b**). Since Et_2O can coordinate to a silyl Lewis acid, a highly reactive silyloxycarbenium cation, $R^3_3Si–OEt_2^+$ [counteranion]$^-$,[17] may be generated in the reaction medium, especially with the low nucleophilic counteranion $^-NTf_2$.

In this reaction pathway ***E***, two possible counteranions could be possible. One is the silicate anion **25**, which bears an NTf_2 group on the silyl aldolate, the other is $^-NTf_2$, which is released from the silyl Lewis acid. In both cases, it is difficult to distinguish path ***E*** from path ***D***. However, we envisaged that reaction path ***D*** could not reasonably explain the results of the control experiments in Scheme 3. The reaction in the presence of 1.0 equiv. of silyl triflylimide should produce a definite amount of silyl aldolate by path ***D***, which bears the silyl group of silyl triflylimide. The real activation species in path ***E*** would be the silyloxycarbenium cation intermediate **24** or **26**, and either would be expected to be a stronger Lewis acid than Me_3SiNTf_2 and $tBuMe_2SiNTf_2$.[17] Our proposed mechanism ***E*** and our hypothesis satisfactorily interprets all the control experiments and the double-label crossover experiments.

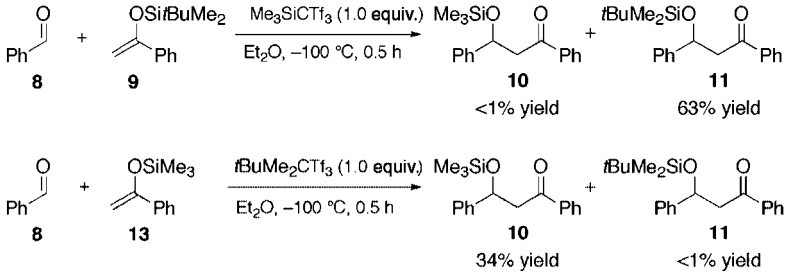


Scheme 5.

Mechanistic Study on the R_3SiCTf_3-Induced Mukaiyama Aldol Reaction

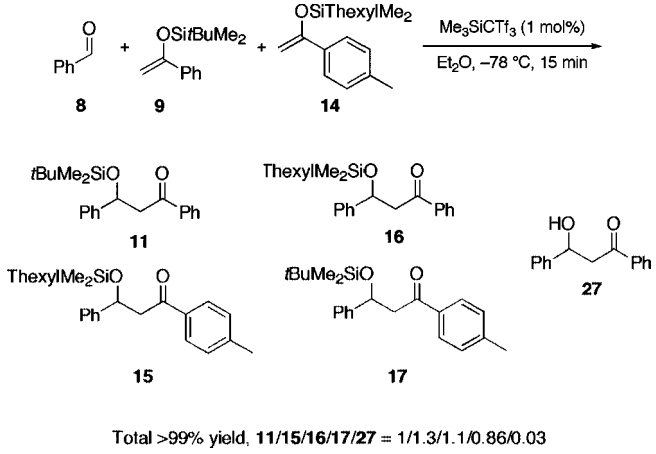
Next, the mechanistic study of the R_3SiCTf_3-induced Mukaiyama aldol reaction was inspected. Me_3SiCTf_3 and tBuMe$_2$SiCTf$_3$ were prepared in situ by the treatment of Me_3SiCl and tBuMe$_2$SiCl with $AgCTf_3$[18] in Et_2O at room temperature, respectively, and were used without further purifications. The control experiments were conducted in a manner similar to that for R_3SiNTf_2 (Scheme 6). In the case of the reaction of tBuMe$_2$Si enol ether **9** with benzaldehyde (**8**) in the presence of 1.0 equiv. of Me_3SiCTf_3, tBuMe$_2$Si aldolate **11** was produced exclusively in 63% yield. No Me_3Si aldolate was detected by ^{1}H NMR spectroscopy or MS analysis. In contrast, the use of 1.0 equiv. of tBuMe$_2$SiCTf$_3$ for the reaction of Me_3Si enol ether **13** with benzaldehyde (**8**) produced Me_3Si aldolate **10** in 34% yield.

A double-label crossover experiment was also conducted for the Me_3SiCTf_3-induced Mukaiyama aldol reaction under the same reaction conditions as those employed for Me_3-



Scheme 6.

$SiNTf_2$ (Scheme 7). Four silyl aldolates (**11**, **15**–**17**) were produced in quantitative yield, and the ratio was similar to the results of Me_3SiNTf_2. The small amount of desilylated aldol **27** was confirmed by GC analysis and may indicate



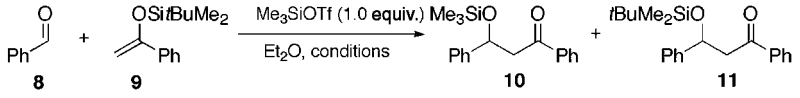
Scheme 7.

the intermediate **25**. The same trend of products in the R_3SiCTf_3- as in the R_3SiNTf_2-induced Mukaiyama aldol reaction led us to the conclusion that the former also proceeds through path ***E***. The low nucleophilicity of $^-CTf_3$ akin to that of $^-NTf_2$ probably contributes to the reaction mechanism.

Mechanistic Study on the R_3SiOTf-Induced Mukaiyama Aldol Reaction

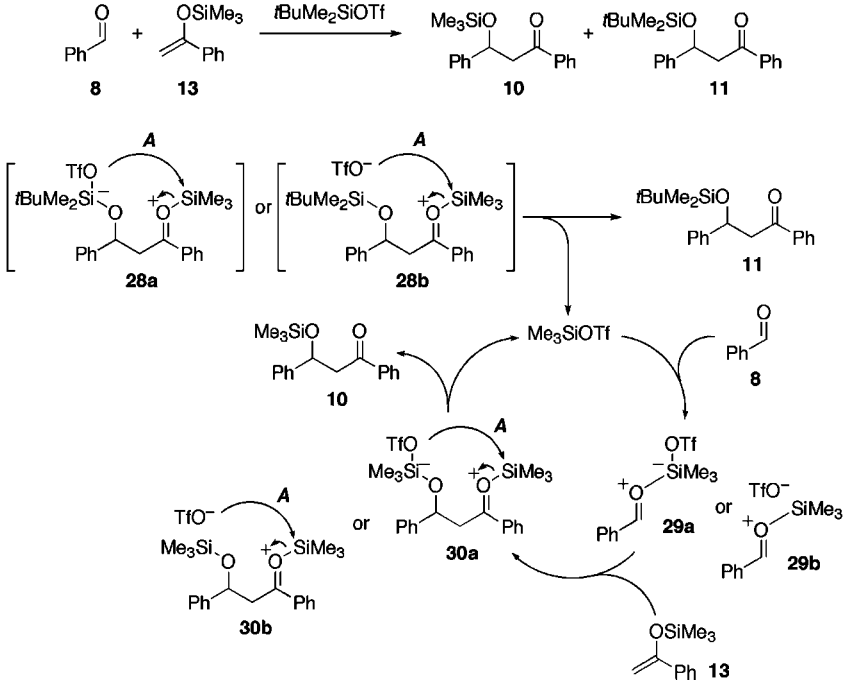
Finally, we performed a mechanistic study of the R_3Si-OTf-induced Mukaiyama aldol reaction.[4,19] The control reactions analogous to those of Scheme 3 were conducted using Me_3SiOTf (Table 2). When the reaction was carried out at –100 °C for 15 min, Me_3Si aldolate **10** was obtained exclusively in 24% yield, along with the starting materials (Table 2, Entry 1). With the Me_3SiNTf_2- or Me_3SiCTf_3-induced reaction, the ratio of silyl aldolates **10** and **11** was completely reversed with respect to that obtained with Me_3-SiOTf. The ratio of produced silyl aldolates suggests that

Table 2. Control experiment for Me_3SiOTf-induced Mukaiyama aldol reaction.



Entry	Conditions	Isolated yield [%]	Ratio **10**/**11**[a]
1	–100 °C, 0.5 h, 0.02 M	24	>99:1
2	–78 °C, 5 h, 0.06 M	61	83:17

[a] Determined by ^1H NMR spectroscopy for the mixture of **10** and **11**.



Scheme 8.

the Me_3SiOTf-induced Mukaiyama aldol reaction proceeds through path ***A***. The starting materials are not completely consumed upon prolonged stirring at –78 °C even with a concentration threefold higher than that in the reaction at –100 °C, and the mixture of **10** and **11** was obtained in 61% yield at a molar ratio of 83:17 (Table 2, Entry 2).

It seems that the result of Entry 2 does not match path ***A*** towing to the generation of tBuMe$_2$Si aldolate **11**. However, further control experiments offered an idea to explain the reaction mechanism adequately by path ***A***. For instance, tBuMe$_2$SiOTf cannot promote the reaction of tBuMe$_2$Si enol ether with benzaldehyde (**8**) under similar reaction conditions as those in Table 2. Furthermore, control experiments of the scrambling for the silyl groups among silyl aldolates **11**, silyl enol ether **9** and Me_3SiOTf showed that neither **9** and Me_3SiOTf nor **11** and Me_3SiOTf were exchanged under similar conditions. On the basis of our observations and Bosnich's proposed pathway,[4] the mechanism for the R_3SiOTf-induced Mukaiyama aldol reaction could be concluded to be an intramolecular transfer of $^-$OTf (path ***A***), and the tBuMe$_2$SiOTf catalysis is shown in Scheme 8 as a model case. From intermediate **28a** or **28b**, Me_3SiOTf is released into the reaction medium by the intramolecular transfer of $^-$OTf, and the reaction is promoted in the same manner. Since Me_3SiOTf possesses a stronger reactivity than tBuMe$_2$SiOTf, the Me_3Si aldolate **10** would be generated through Me_3SiOTf catalysis under the reaction conditions shown in Table 2. In the case of the R_3Si-OTf-induced Mukaiyama aldol reaction, the formation of $Me_3Si{\cdot}OEt_2^+$ with $^-$OTf can be excluded because of the relatively high nucleophilicity of $^-$OTf.[20]

Conclusion

We have demonstrated the diversity of the mechanism for silyl Lewis acid induced Mukaiyama aldol reactions that are dependent on the conjugate base, and have proposed a novel reaction mechanism ***E***. In the case of R_3SiNTf_2- or R_3SiCTf_3-induced Mukaiyama aldol reactions, the low nucleophilicity of their conjugate bases prevent not only the intramolecular transfer of X^- (path ***A***) but also that of the R_3Si group to the carbonyl oxygen atom (path ***B***). On the other hand, the high nucleophilicity of $^-$OTf[17] causes the intramolecular transfer of X^- and generates the silyl Lewis acid derived from silyl enol ether.

Experimental Section

General Remarks: Unless otherwise stated, reactions were performed in flame-dried glassware under argon. Infrared (IR) spectra were recorded with a Shimadzu FTIR-8100 spectrometer and Nicolet 20 SXB FTIR spectrometer, and are reported in reciprocal centimeters (cm^{-1}). ^{1}H NMR spectra were measured with Bruker DMX-500 (500 MHz), 400 (400 MHz), and Varian Gemini-300 (300 MHz) spectrometers at room temperature. Data are reported as follows: chemical shift in ppm from internal Me_4Si (δ = 0.0 ppm) on the δ scale, coupling constant J [Hz], integration, and assignment. ^{13}C NMR spectra were recorded with Bruker DMX-500 (125 MHz) and 400 (100 MHz), and Varian Gemini-300 (75 MHz) spectrometers at room temperature. Chemical shifts are reported in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at δ = 77.00 ppm). Analytical gas–liquid phase chromatography (GC) was performed with a Shimadzu Model GC-17A Ver. 3 instrument with a flame-ionization detector and a capillary column of TC-1 (100% dimethylpolysiloxane, 0.25 mm × 30 m, GL Sciences Inc.) using helium as carrier gas (116.0 kPa). Measurement conditions: Injection temp. 150 °C; column temp. 70 °C for 5 min, +10 °C/min for 18 min, and 250 °C for 7 min. High-resolution mass spectra data were obtained from the Research Resources Center Mass Spectrometry Laboratory at University of Illinois at Chicago. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254 0.25 mm) were used. The products were purified by flash column chromatography on silica gel (E. Merck 9325). In experiments that required dry solvents, CH_2Cl_2, Et_2O and THF were stored under dry argon after being distilled from calcium hydride (CH_2Cl_2) or sodium metal using benzophenone ketyl as an initiator (Et_2O and THF), and were then used. Simple chemicals (if not described in this Exp. Sect.) were purchased and used. $AgNTf_2$ and $AgCTf_3$ were prepared according to Shreeve's procedure.[18,21]

Preparation of Me_3SiNTf_2:[6] Me_3SiNTf_2 was prepared from freshly distilled Me_3SiCl (1.2 equiv.) and $AgNTf_2$ (1.0 equiv.) in CH_2Cl_2 and purified by distillation (80–84 °C, 7 Torr). Me_3SiNTf_2 was also prepared from freshly distilled Me_3SiCl (1.2 equiv.) and $AgNTf_2$ (1 equiv.) in Et_2O and used for the reaction without further purification.

Preparation of tBuMe$_2$SiNTf$_2$, Me$_3$SiCTf$_3$, and tBuMe$_2$SiCTf$_3$: These silyl Lewis acids were prepared in situ according to the procedure for Me_3SiNTf_2 using the corresponding silyl chloride and silver salt.

General Procedure for the Control Experiments (Schemes 3 and 6, Table 2): To a solution of in situ prepared tBuMe$_2$SiNTf$_2$ (1.0 mmol) in dry Et_2O (50 mL) was added freshly distilled benzaldehyde (**8**, 102 μL, 1.0 mmol) at –100 °C. Subsequently, Me_3Si enol ether **13** (281 mg, 1.2 mmol) was added in a dropwise fashion at the same temperature. After stirring for 0.5 h, pyridine (200 μL) and saturated aqueous $NaHCO_3$ (20 mL) were added. The mixture was warmed to room temperature and extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried with Na_2SO_4, concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 10:1) to give Me_3Si aldolate **10** (185 mg, 62% yield). The corresponding tBuMe$_2$Si aldolate **11** was not formed in a detectable amount (^{1}H NMR and GC analysis).

General Procedure for the Silyl Group Scrambling Control Experiments (Schemes 3, 4, 6 and 7, Table 2): To a solution of 3-(*tert*-butyldimethylsilyloxy)-1,3-diphenylpropan-1-one (**11**, 340 mg, 1.0 mmol) in Et_2O (50 mL) was added freshly distilled Me_3SiOTf (184 μL, 1.0 mmol) at –100 °C. The reaction mixture was stirred for 0.5 h, and quenched with pyridine (200 μL) and saturated aqueous $NaHCO_3$ (20 mL). The mixture was then warmed to room temperature and extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried with Na_2SO_4, and concentrated under reduced pressure. The corresponding Me_3Si aldolate **10** was not formed in a detectable amount (^{1}H NMR and GC analysis).

Procedure for the Silyl Group Scrambling Control Experiments of Silyl Enol Ether 9 and 14 (Schemes 4 and 7): To a solution of **9** (1.8 mmol, 422 mg), **14** (1.8 mmol, 498 mg), and Me_3SiNTf_2 (0.03 mmol, prepared in situ by the treatment of Me_3SiCl and $AgNTf_2$) in Et_2O (6.0 mL) was added benzaldehyde (0.3 mmol,

30 μL) at –78 °C. The reaction mixture was stirred at –78 °C for 15 min and quenched with pyridine (5 drops) followed by saturated aqueous $NaHCO_3$ (15 mL). The mixture was warmed to room temperature and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated. No silyl group exchange was observed by ^1H NMR analysis of the residue.

General Procedure for the Double-Label Crossover Experiment (Schemes 4 and 7): To a solution of Me_3SiNTf_2 (11 mg, 0.03 mmol), silyl enol ether **9** (421 mg, 1.8 mmol), and silyl enol ether **14** (497 mg, 1.8 mmol) in Et_2O (6 mL) was added freshly distilled benzaldehyde (**8**, 305 μL, 3.0 mmol) at –78 °C. The reaction mixture was stirred for 15 min, quenched with pyridine (5 drops) followed by saturated aqueous $NaHCO_3$ (5 mL), warmed to room temperature, and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography on silica gel (hexane/EtOAc, 50:1) to give a mixture of **11**, **15**, **16**, and **17** (1.15 g, >99% yield). The ratio of products was determined as 1:1.0:0.89:0.81 by ^1H NMR and GC analysis. The GC peaks were assigned on the basis of the $[M – 15]^+$ or $[M + H]^+$ peak as well as expected fragmentation patterns. GC/MS: *t*BuMe$_2$Si aldolate **11**; t_R = 20.5 min, *m*/*z* = 341 $[M + H]^+$. ThexylMe$_2$Si aldolate **15**; t_R = 22.8 min, *m*/*z* = 383 $[M + H]^+$. ThexylMe$_2$Si aldolate **16**; t_R = 22.5 min, *m*/*z* = 353 $[M – 15]^+$. *t*BuMe$_2$Si aldolate **17**; t_R = 20.9 min, *m*/*z* = 355 $[M + H]^+$.

General Procedure for the Mukaiyama Aldol Reaction (Table 1): To a solution of in situ prepared *t*BuMe$_2$SiNTf$_2$ (0.03 mmol) in Et_2O (2 mL) was added freshly distilled (1-cyclohexenyloxy)trimethylsilane (**18**, 233 μL, 1.2 mmol) at –78 °C, followed by benzaldehyde (**8**, 102 μL, 1.0 mmol). The reaction mixture was stirred at –78 °C for 20 min, quenched with pyridine (5 drops) and saturated aqueous $NaHCO_3$ (5 mL), and extracted with Et_2O (2 × 10 mL). The combined organic layers were dried with Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography on silica gel (hexane/EtOAc, 50:1) to give a diastereomer mixture of the corresponding silyl aldolate (277 mg, >99% yield, *syn*/*anti* = 62:38 determined by ^1H NMR). In all cases, the diastereoselectivities were determined by ^1H NMR of the diastereomer mixtures, according to reported values.

Dimethyl(thexyl)([1-(*p*-tolyl)vinyloxy]silane (14): To a solution of dimethyl(thexyl)silyl chloride (3.5 mL, 18 mmol) and silver trifluoromethanesulfonate (4.2 g, 16.5 mL) in CH_2Cl_2 (20 mL) was added methyl 4-methylphenyl ketone (2.0 mL, 15 mmol) and triethylamine (4.2 mL, 30 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 3 h, quenched with a saturated aqueous $NaHCO_3$ solution (10 mL), and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried with Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography on silanized silica gel (column wrapped with a dry ice jacket, hexane/EtOAc, 50:1) to give **14** (3.36 g, 81% yield) as a colorless oil. IR (film): $\tilde{\nu}$ = 2959, 1614, 1511, 1465, 1314, 1301, 1183, 1111, 832, 781 cm^{-1}. ^1H NMR (300 MHz, room temp., $CDCl_3$): δ = 0.23 (s, 6 H, Me), 0.95 (m, 12 H, Me), 1.74 (m, 1 H, C*H* for thexyl group), 2.35 (s, 3 H, ArCH_3), 4.35 (d, *J* = 1.5 Hz, 1 H, CH_2), 4.83 (d, *J* = 1.5 Hz, 1 H, CH_2), 7.13 (d, *J* = 8.7 Hz, 2 H, *m*-H for *p*-tolyl group), 7.50 (d, *J* = 8.7 Hz, 2 H, *o*-H for *p*-tolyl group) ppm. ^{13}C NMR (100 MHz, room temp., $CDCl_3$): δ = –2.7 (*C*H$_3$Si), 18.5 [(*C*H$_3$)$_2$CSi], 20.2 [(CH$_3$)$_2$CH], 21.2 (*C*H$_3$Ph), 25.1 [SiC(CH$_3$)$_2$CH], 33.9 [(CH$_3$)$_2$*C*H], 90.3 (*C*H$_2$), 125.2 (*o*-*C*H for *p*-tolyl group), 128.7 (*m*-*C*H for *p*-tolyl group), 135.2 [*C*–CSi(CH$_2$)], 137.9 (*p*-*C*H for *p*-tolyl group), 155.9 [*p*-tolyl*C*–Si(CH$_2$)] ppm.

3-[Dimethyl(thexyl)silyloxy]-3-phenyl-1-(*p*-tolyl)propan-1-one (15): To a solution of in situ prepared Me_3SiNTf_2 (ca. 0.005 mmol) and silyl enol ether **14** (166 mg, 0.6 mmol) in Et_2O (1 mL) was added freshly distilled benzaldehyde (**8**, 51 μL, 0.5 mmol) at –78 °C. The reaction mixture was stirred for 15 min, quenched with pyridine (2 drops) and a saturated aqueous $NaHCO_3$ solution (5 mL), then warmed to room temperature, and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried with Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography on silica gel (hexane/EtOAc, 50:1) to give **15** (195 mg, 99% yield) as a colorless oil. TLC (hexane/EtOAc, 4:1): R_f = 0.64. GC: t_R = 22.8 min. IR (film): $\tilde{\nu}$ = 2959, 1684, 1607, 1254, 1089, 1071, 939, 831, 810, 777 cm^{-1}. ^1H NMR (300 MHz, room temp., $CDCl_3$): δ = –0.20 (s, 3 H, Me), –0.01 (s, 3 H, Me), 0.71 (s, 6 H, Me), 0.77 (d, *J* = 6.9 Hz, 3 H, Me), 0.78 (d, *J* = 6.9 Hz, 3 H, Me), 1.51 (sept, *J* = 6.9 Hz, 1 H, CH for thexyl group), 2.41 (s, 3 H, ArCH_3), 2.92 (dd, *J* = 3.9, 15.0 Hz, 1 H, CH_2), 3.55 (dd, *J* = 8.4, 15.0 Hz, 1 H, CH_2), 5.35 (dd, *J* = 3.9, 8.4 Hz, 1 H, CH), 7.23–7.42 (m, 7 H, Ar), 7.86 (d, *J* = 8.1 Hz, 2 H, Ar-*H* for phenyl) ppm. $C_{24}H_{34}O_2Si$ (382.64): calcd. C 75.34, H 8.96; found C 75.32, H 8.99.

3-(*tert*-Butyldimethylsilyloxy)-3-phenyl-1-(*p*-tolyl)propan-1-one (17): To a solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.98 mL, 8.3 mmol) and triethylamine (2.1 mL, 15 mmol) in CH_2Cl_2 (20 mL) was added methyl 4-methylphenyl ketone (1.0 mL, 7.5 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 3 h, quenched with a saturated aqueous $NaHCO_3$ solution (10 mL), and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried with Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography on silanized silica gel (column wrapped with a dry ice jacket, pentane) to give *tert*-butyldimethyl(1-*p*-tolylvinyloxy)silane (1.16 g, 63% yield) as a colorless oil. IR (film): $\tilde{\nu}$ = 2930, 2361, 1616, 1315, 1302, 1254, 1111, 1014, 836, 780 cm^{-1}. ^1H NMR (400 MHz, room temp., $CDCl_3$): δ = 0.20 (s, 6 H, CH_3Si), 1.00 [s, 9 H, (CH$_3$)C], 2.34 (s, 3 H, ArCH_3), 4.36 (d, *J* = 1.6 Hz, 1 H, CH_2), 4.84 (d, *J* = 1.6 Hz, 1 H, CH_2), 7.12 (d, *J* = 6.5 Hz, 2 H, *m*-*H* for *p*-tolyl group), 7.50 (d, *J* = 6.5 Hz, 2 H, *o*-*H* for *p*-tolyl group) ppm. ^{13}C NMR (100 MHz, room temp., $CDCl_3$): δ = –4.6 (*C*H$_3$Si), 21,2 [(CH$_3$)$_3$*C*Si], 25.7 [(*C*H$_3$)$_3$CSi], 90.2 (*C*H$_2$), 125.2 (*o*-*C*H for *p*-tolyl group), 128.7 (*m*-*C*H for *p*-tolyl group), 135.0 [*C*–CSi(CH$_2$)], 138.0 (*p*-*C* for *p*-tolyl group), 156.0 (*p*-tolyl*C*–Si) ppm. The title compound was synthesized according to the analoguous procedure for **15** using *tert*-butyldimethyl(1-*p*-tolylvinyloxy)silane instead of **14**. TLC (hexane/EtOAc, 4:1): R_f = 0.74. GC: t_R = 20.9 min. IR (film): $\tilde{\nu}$ = 2955, 1686, 1607, 1256, 1092, 1071, 939, 835, 808, 779 cm^{-1}. ^1H NMR (300 MHz): δ = –0.18 (s, 3 H, Me), –0.09 (s, 3 H, Me), 0.75 (s, 9 H, *t*Bu), 2.41 (s, 3 H, ArCH_3), 2.92 (dd, *J* = 3.9, 15.3 Hz, 1 H, CH_2), 3.55 (dd, *J* = 8.7, 15.3 Hz, 1 H, CH_2), 5.35 (dd, *J* = 3.9, 8.7 Hz, 1 H, CH), 7.23–7.43 (m, 7 H, Ar), 7.87 (d, *J* = 8.1 Hz, 2 H, Ar-*H* for phenyl) ppm. $C_{22}H_{30}O_2Si$ (354.56): calcd. C 74.53, H 8.53; found C 74.67, H 8.52.

Acknowledgments

Support for this research was provided by the SORST project of the Japan Science and Tecnology Corp. (JST), National Institute of Health (NIH) GM068433-01, and a starter grant from the University of Chicago.

[1] E. M. Carreira, in: *Comprehensive Asymmetric Catalysis III* (Ed.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, Berlin, Heidelberg, **1999**, p. 997.
[2] E. M. Carreira, R. A. Singer, *Tetrahedron Lett.* **1994**, *35*, 4323–4326.

[3] S. E. Denmark, C.-T. Chen, *Tetrahedron Lett.* **1994**, *35*, 4327–4330.
[4] T. K. Hollis, B. Bosnich, *J. Am. Chem. Soc.* **1995**, *117*, 4570–4581.
[5] There may be a rapid equilibration between an oxetane intermediate and **5a** or **5b**:W. W. Ellis, B. Bosnich, *Chem. Commun.* **1998**, 193–194.
[6] B. Mathieu, L. Ghosez, *Tetrahedron Lett.* **1997**, *38*, 5497–5500.
[7] A. Ishii, O. Kotera, T. Saeki, K. Mikami, *Synlett* **1997**, 1145–1146.
[8] N. Kuhnert, J. Peverley, J. Robertson, *Tetrahedron Lett.* **1998**, *39*, 3215–3216.
[9] J. Cossy, F. Lutz, V. Alauze, C. Meyer, *Synlett* **2002**, 45–48.
[10] K. Ishihara, Y. Hiraiwa, H. Yamamoto, *Synlett* **2001**, 1851–1854.
[11] M. G. Davidson, P. R. Raithby, A. L. Johnson, P. D. Bolton, *Eur. J. Inorg. Chem.* **2003**, 3445–3452.
[12] L. Turowsky, K. Seppelt, *Inorg. Chem.* **1988**, *27*, 2135–2137.
[13] F. J. Waller, A. G. M. Barrett, D. C. Braddock, D. Ramprasad, R. M. McKinnell, A. J. P. White, D. J. Williams, R. Ducray, *J. Org. Chem.* **1999**, *64*, 2910–2913.
[14] I. A. Koppel, R. W. Taft, F. Anvia, S.-Z. Zhu, L.-Q. Hu, K.-S. Sung, D. D. DesMarteau, L. M. Yagupolskii, Y. L. Yagupolskii, N. V. Ignat'ev, N. V. Kondratenko, A. Y. Volkonskii, V. M. Vlasov, R. Notario, P.-C. Maria, *J. Am. Chem. Soc.* **1994**, *116*, 3047–3057.
[15] K. Ishihara, Y. Hiraiwa, H. Yamamoto, *Chem. Commun.* **2002**, 1564–1565.
[16] These scrambling experiments exclude the possibility for path ***C*** and ***D*** in Scheme 1.
[17] D. D. Dilman, S. L. Loffe, *Chem. Rev.* **2003**, *103*, 733–772.
[18] K. Ishihara, Y. Hiraiwa, H. Yamamoto, *Synlett* **2000**, 80–82.
[19] S. Murata, M. Suzuki, R. Noyori, *Tetrahedron* **1988**, *44*, 4259–4275.
[20] M. B. Berry, R. J. Griffiths, J. A. Howard, J. M. A. Leech, P. G. Steel, D. S. Yufit, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3645–3650.
[21] A. Vij, Y. Y. Zheng, R. L. Kirchmeier, J. M. Shreeve, *Inorg. Chem.* **1994**, *33*, 3281–3288.

Received: October 29, 2005
Published Online: February 9, 2006

