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Crucial role of the ligand of silyl Lewis acid in the Mukaiyama aldol reaction†

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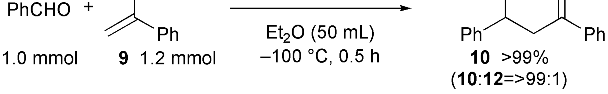
The Me_3SiX-induced Mukaiyama aldol reaction proceeds through each catalytic cycle under the influence of X^-: the silyl group of Me_3SiNTf_2 does not release from $^-NTf_2$ and that of silyl enol ether intermolecularly transfers to the product, while the silyl group of Me_3SiOTf remains in the product and that of the silyl enol ether becomes the catalyst for the next catalytic cycle.

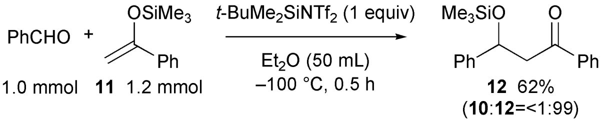
Ghosez[1a] and Mikami[1b] have independently introduced Me_3SiNTf_2 as a much more powerful carbonyl-activating reagent than Me_3SiOTf. Very recently, we demonstrated the extremely high activity of Me_3SiNTf_2 as a catalyst for the Mukaiyama aldol and Sakurai–Hosomi allylation reactions of not only aldehydes but also ketones.[2,3] We report here that the Me_3SiX-induced Mukaiyama aldol reaction proceeds through each catalytic cycle under the influence of its ligand (X): specifically, there is a significant difference between $^-NTf_2$ and ^-OTf, in that the silyl group of Me_3SiNTf_2 does not release from its ligand and that of silyl enol ether intermolecularly transfers to the product, while the silyl group of Me_3SiOTf remains in the product and that of the silyl enol ether becomes the catalyst for the next catalytic cycle.[4]

The three plausible reaction pathways for the Me_3SiX-induced Mukaiyama aldol reaction are outlined in Fig. 1.[5] In the first stage of catalysis, the addition of a trialkylsilyl enol ether **2** to a Me_3Si-activated aldehyde **1** generates a siloxocarbenium ion intermediate **3**. In *path A*, R_3SiX is released into the reaction medium to give the trimethylsilyl aldolate **4** by the intramolecular transfer of X^-.[6] Thus, R_3SiX becomes the catalyst for the next catalytic cycle.[7] In *path B*, Me_3SiX is released into the reaction medium to give the trialkylsilyl aldolate **5** by the intramolecular transfer of R_3Si^+.[6,8] In *path C*, co-ordinated aldehyde as in **6** or **7**, which is activated by penta- or tetra-coordination[4,9] of R_3Si^+, reacts with **2** through the intermolecular silyl transfer of R_3Si^+. In this catalytic process, **5** may be obtained as a major product.[10]

First, the mechanistic details of the Me_3SiNTf_2[1a,11]-induced reaction were investigated. To clarify whether transformation from **2** to a silyl aldolate occurs through $^-NTf_2$ transfer (*path A*) or $^+SiR_3$ transfer (*path B or C*), the reaction of *tert*-butyldimethylsilyl enol ether **9** derived from acetophenone with benzaldehyde was carried out in the presence of 1 equiv. of Me_3SiNTf_2 at −100 °C for 0.5 h. Regardless of the order of the addition of substrates and Me_3SiNTf_2, only *tert*-butyldimethylsilyl aldolate **10** was obtained in high yield [eqn. (1)]. In contrast, the reaction of trimethylsilyl enol ether **11** with benzaldehyde in the presence of 1 equiv. of $t\text{-}BuMe_2SiNTf_2$ gave only trimethylsilyl aldolate **12** in moderate yield [eqn. (2)]. Control experiments for eqn. (1) showed that neither **9** and Me_3SiNTf_2 nor **12** and $t\text{-}BuMe_2SiNTf_2$ exchanged under similar conditions. These experimental results exclude *path A*. Although *path C* is also unlikely since **12** was not detected by GC analysis [eqn. (1)], we can not exclude *path C* because the equilibration between benzaldehyde and **1** may be quite fast, and the aldol reaction induced by *tert*-butyldimethylsiloxocarbenium ions **3** and **8** could be much faster than that induced by Me_3SiNTf_2. In fact, Me_3SiNTf_2 is an extraordinarily active catalyst,[1,2] and its high turnover frequency can be reasonably explained by a $^+SiR_3$-induced cascade process which avoids the regeneration of Me_3SiNTf_2.



(1)



(2)

For a crossover experiment,[4] two silyl enol ethers **9** and **13** with comparable steric and electronic properties were combined with benzaldehyde [eqn. (3)]. Benzaldehyde was added to a solution of a 1 : 1 mixture of **9** and **13** (0.6 equiv. of each) in the presence of 1 mol% of Me_3SiNTf_2 at −78 °C. The product composition was determined by GC analysis. A mixture of

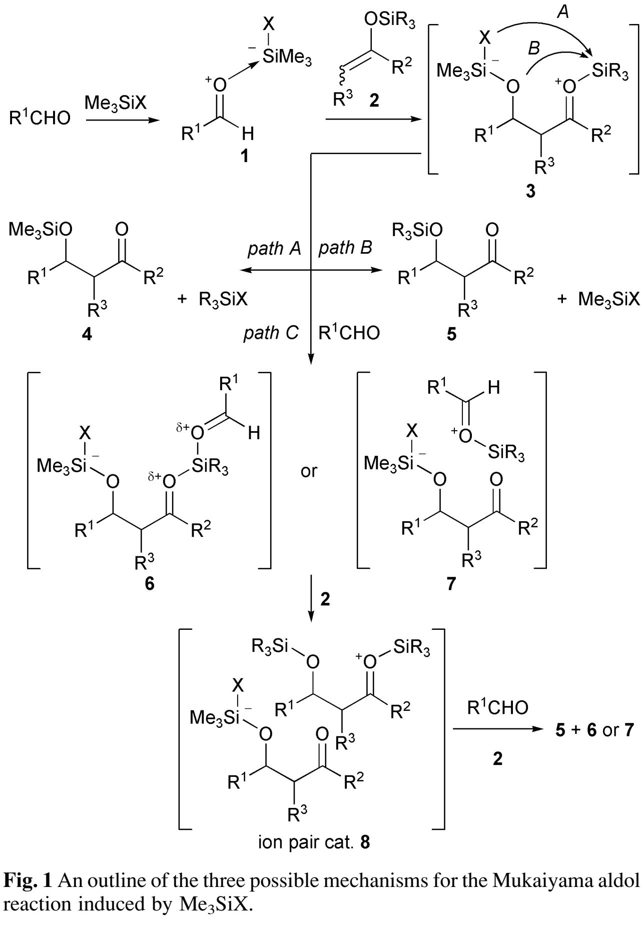


Fig. 1 An outline of the three possible mechanisms for the Mukaiyama aldol reaction induced by Me_3SiX.

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† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b2/b203838b/

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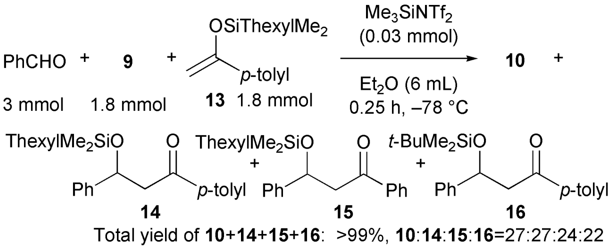
scrambled silyl ethers was isolated in a ratio of 27:27:24:22 (**10**:**14**:**15**:**16**). Control experiments showed that neither the starting silyl enol ethers nor the silylated aldol products exchanged under similar reaction conditions. Based on these observations, *path B* was unambiguously precluded. Therefore, it is likely that the Me_3SiNTf_2-induced reaction occurs through *path C*.



(3)

The *syn*/*anti* selectivities in the aldol reactions of (*E*)- and (*Z*)-silyl enol ethers induced by silyltriflylimides were investigated (Table 1). Similar *syn*/*anti* ratios of silyl aldolates, **19** and **20**, were obtained independent of the trialkylsilyl group of the silyltriflylimides. On the other hand, the ratios were correlative to the trialkylsilyl group of silyl enol ethers. These results also support *path C*.

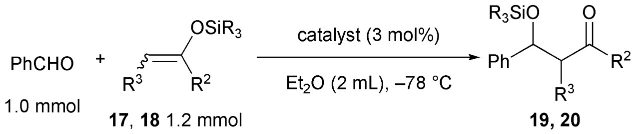
Next, we performed a mechanistic study of the Me_3SiOTf-induced Mukaiyama aldol reaction.[12] Reactions analogous to eqn. (1) were conducted using Me_3SiOTf [eqn. (4)]. A mixture of **10** and **12** was obtained in 24% yield at a molar ratio of 1:99 under the same conditions with eqn. (1). The starting materials were not completely consumed upon prolonged stirring at −78 °C with a concentration three-fold higher than that in eqn. (1), and a mixture of **10** and **12** was obtained in 61% yield at a molar ratio of 17:83 after 5 h at −78 °C. The reaction of **9** with benzaldehyde did not proceed at −100 °C in the presence of *t*-$BuMe_2SiOTf$ in a control experiment for eqn. (4). Further control experiments for eqn. (4) showed that neither **9** and Me_3SiOTf nor **10** and Me_3SiOTf exchanged under similar conditions. These experimental results strongly support the mechanism (*path A*) proposed by Hollis and Bosnich.[4d]

$$\underset{1.0\ \text{mmol}}{\text{PhCHO}} + \underset{1.2\ \text{mmol}}{\mathbf{9}} \xrightarrow[\text{Et}_2\text{O}]{\text{Me}_3\text{SiOTf (1 equiv)}} \mathbf{10} + \mathbf{12} \qquad (4)$$

Et_2O (50 mL), –100 °C, 0.5 h: 24% yield, **10**:**12**=1:99
Et_2O (12.5 mL), –78 °C, 5 h: 61% yield, **10**:**12**=17:83

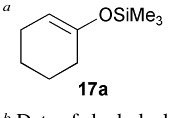
The present observations indicate that the ligand of silyl Lewis acid plays a crucial role in the aldol reaction. The transfer of X^- from **3** is expected to occur by electrophilic attack of the '$R_3Si–O^+$ silicon' of **3**. In the Me_3SiOTf-induced reaction, R_3SiOTf would be generated by electrophilic attack of the '$R_3Si–O^+$ silicon' to the 'S = O oxygens' or the 'S–O oxygen' of ^-OTf (*path A*). In the Me_3SiNTf_2-induced reaction, on the contrary, less nucleophilicity[14] and/or more bulkiness of $^-NTf_2$ may suppress the electrophilic attack of the '$R_3Si–O^+$ silicon' to the nitrogen[11] or oxygen atoms[13] of $^-NTf_2$, and may increase Lewis acidity of siloxocarbenium ions **3** and **8** (*path C*).

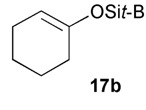
Table 1 *Syn*/*anti* selectivity in the Mukaiyama aldol reaction

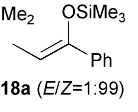


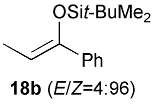
Silyl enol ether[a]	Catalyst	Silyl aldolates Yield (%)	 *Syn*:*Anti*
17a	Me_3SiNTf_2	**19a**, 97	60:40
17a	*t*-$BuMe_2SiNTf_2$	**19a**, >99	62:38
17b	Me_3SiNTf_2	**19b**, >99	52:48
17b	*t*-$BuMe_2SiNTf_2$	**19b**, >99	51:49
18a	Me_3SiNTf_2	**20a**, 90 (1)[b][9][c]	61:39 (48:52)[b]
18a	*t*-$BuMe_2SiNTf_2$	**20a**, 89 (2)[b][12][c]	58:42 (45:55)[b]
18b	Me_3SiNTf_2	**20b**, >99	87:13
18b	*t*-$BuMe_2SiNTf_2$	**20b**, >99	87:13

[a]


17a

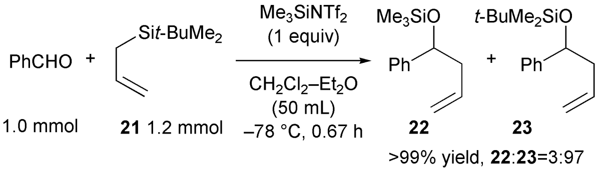

17b


18a (*E*/*Z*=1:99)


18b (*E*/*Z*=4:96)

[b] Data of alcohol adducts are given in parentheses. [c] Yields of dimeric ethers of alcohols are given in brackets.[2]

Lastly, Sakurai–Hosomi allylation reaction induced by Me_3SiNTf_2 also occurs through $^+SiR_3$ transfer, according to results of a stoichiometric experiment [eqn. (5)].[2]



(5)

These findings may provide a basis for the future development of not only chiral silyl Lewis acid catalysts but also other chiral metal catalysts for carbon–carbon bond-forming reactions of silyl nucleophiles with carbonyl compounds.[15]

Notes and references

1 (*a*) B. Mathieu and L. Ghosez, *Tetrahedron Lett.*, 1997, **38**, 5497; (*b*) A. Ishii, O. Kotera, T. Saeki and K. Mikami, *Synlett*, 1997, 1145.

2 K. Ishihara, Y. Hiraiwa and H. Yamamoto, *Synlett*, 2001, 1851.

3 (*a*) For carbon–carbon bond forming reactions catalyzed by $HNTf_2$, see: N. Kuhnert, J. Peverley and J. Robertson, *Tetrahedron Lett.*, 1998, **39**, 3215; (*b*) J. Cossy, F. Lutz, V. Alauze and C. Meyer, *Synlett*, 2002, 45.

4 (*a*) For mechanistic studies on the Mukaiyama aldol reaction induced by metal triflates, metal perchlorates, or trityl salts, see: E. M. Carreira, in *Comprehensive Asymmetric Catalysis III*, eds. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, Heidelberg, 1999, p. 997; (*b*) E. M. Carreira and R. A. Singer, *Tetrahedron Lett.*, 1994, **45**, 4323; (*c*) S. E. Denmark and C.-T. Chen, *Tetrahedron Lett.*, 1994, **35**, 4327; (*d*) K. T. Hollis and J. Bosnich, *J. Am. Chem. Soc.*, 1995, **117**, 4570.

5 There may be a rapid equilibration between **3** and an oxetane intermediate: W. W. Ellis and B. Bosnich, *Chem. Commun.*, 1998, 193.

6 The intermolecular transfer of X^- or R_3Si^+ is unlikely due to unfavorable entropic and steric factors.

7 This means that chiral silyl Lewis acids cannot be used as enantioselective catalysts.

8 The catalytic cycle through *path B* is essential for the rational design of chiral silyl Lewis acid catalysts.

9 (*a*) For the importance of pentacoordinated silicon species as reactive intermediates, see: R. Damrauer, C. H. DePuy and V. M. Bierbaum, *Organometallics*, 1982, **1**, 1553; (*b*) A. R. Bassindale and T. Stout, *J. Organomet. Chem.*, 1982, **238**, C41; (*c*) J. C. Sheldon, R. N. Hayes and J. H. Bowie, *J. Am. Chem. Soc.*, 1984, **106**, 7711; (*d*) R. J. P. Corriu, C. Guérin and J. J. E. Moreau, *Top. Stereochem.*, 1984, **15**, 43.

10 It may be relatively difficult to design chiral silyl Lewis acid catalysts for the catalytic cycle through *path C*.

11 Me_3SiNTf_2, which was prepared from Me_3SiCl and $AgNTf_2$ in dichloromethane, was purified by distillation (80–84 °C , 7 torr). Its *N*-silyl structure has been determined on the basis of ^{13}C and ^{29}Si NMR spectra. A. Vij, Y. Y. Zheng, R. L. Kirchmeier and J. M. Shreeve, *Inorg. Chem.*, 1994, **33**, 3281.

12 S. Murata, M. Suzuki and R. Noyori, *Tetrahedron*, 1988, **44**, 4259.

13 Me_3SiNTf_2 exists in an *N*-silyl structure while *t*-$BuMe_2SiNTf_2$ and *i*-Pr_3SiNTf_2 exist in an *O*-silyl structure according to ^{19}F NMR analysis. G. Simchen and S. Jonas, *J. Prakt. Chem.*, 1998, **340**, 506.

14 According to a report about the relative gas-phase acidities of Brønsted superacids, $HNTf_2$ ($G_{acid} = 291.8$ kcal mol^{-1}) is a stronger acid than TfOH ($G_{acid} = 299.5$ kcal mol^{-1}). Therefore, it is expected that the nucleophilicity of $^-NTf_2$ is lower than that of ^-OTf by delocalization: I. A. Koppel, R. W. Taft, F. Anvia, S.-Z. Zhu, L.-Q. Hu, K.-S. Sung, D. D. DeaMarteau, L. M. Yagupolskii, Y. L. Yagupolskii, N. V. Ignat'ev, N. V. Kondratenko, A. Y. Volkonskii, V. M. Vlasov, R. Notario and P.-C. Maria, *J. Am. Chem. Soc.*, 1994, **116**, 3047.

15 In this paper, diethyl ether was used uniformly as a solvent in order to make it easy to control the catalytic activity of silyl Lewis acids.