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Chemoselective silyl transfer in the Mukaiyama aldol reaction promoted by super silyl Lewis acid†

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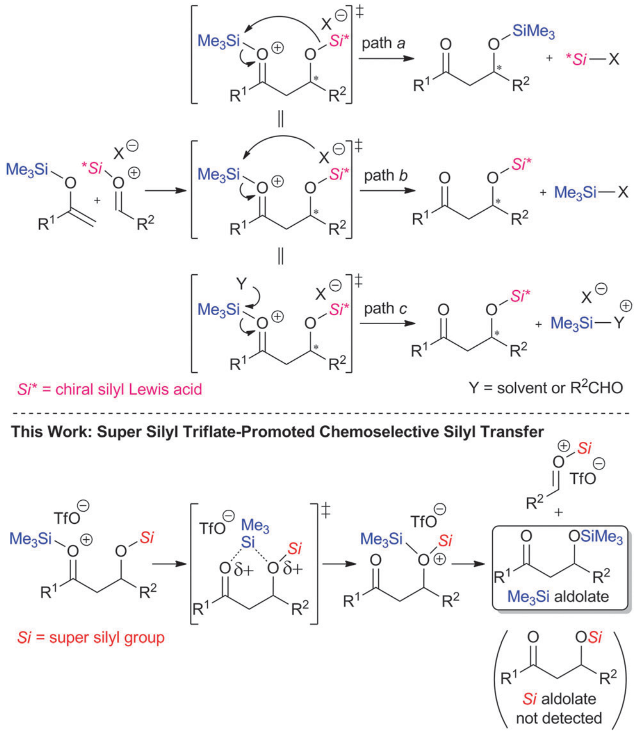
In the silyl Lewis acid-promoted Mukaiyama aldol reaction, the steric and electronic properties of the silyl group on the silyl Lewis acid influence the reaction mechanism and product distribution. When super silyl triflates such as $(TMS)_3SiOTf$ and $(TES)_3SiOTf$ are used as Lewis acids, the silyl group of the silyl enol ether chemoselectively transfers to the product. The mechanistic details have been investigated using density functional theory (DFT) calculations.

Silyl Lewis acids have been widely utilized in synthetic organic chemistry.[1] In 2002, we demonstrated that Me_3SiNTf_2 (ref. 2) shows a strong catalytic activity for the Mukaiyama aldol reaction[3,4] of not only aldehydes but also ketones.[5] However, developing a chiral silyl Lewis acid catalyst that works well for the enantioselective version is still challenging. The complication in the reaction is due to the fact that two different silyl Lewis acids can be generated *in situ*: one from the catalyst and one from the silyl enol ether. The three plausible reaction pathways for the chiral silyl Lewis acid-catalyzed Mukaiyama aldol reaction are outlined in Scheme 1. In the first step, the siloxycarbenium intermediate is generated *via* the addition of the silyl enol ether to the aldehyde activated by the chiral silyl Lewis acid catalyst. In path a, intramolecular transfer of Me_3Si^+ occurs to provide the desired aldolate product and the original chiral Lewis acid (Si*–X). In contrast, Me_3SiX can be released *via* the intramolecular transfer of X^- in path b. Thus, achiral Me_3SiX becomes the catalyst for the next catalytic cycle leading to a racemic product. In path c, another aldehyde or coordinating solvent intermolecularly attacks Me_3Si^+ of the intermediate, giving Me_3Si^+-activated aldehyde or solvent coordinated Me_3SiX. In this catalytic process, racemic Me_3Si aldolate would be obtained as the major product. This implies that only path a can be considered as a desirable pathway for the realization of chiral silyl Lewis acid-catalyzed asymmetric Mukaiyama aldol reaction.[6] Therefore, we attempted to discover the factors that govern the transfer of Me_3Si^+ and X^-. According to the double-label crossover experiment similar to that described by Carreira[7] and Denmark,[8] we have already demonstrated the diversity of the mechanism for silyl Lewis acid-promoted Mukaiyama aldol reactions that are dependent on the counteranion.[9–11] However, there has been no report on the influence of the silyl group of the silyl Lewis acids on the reaction mechanism and product distribution. Herein, we wish to report that the use of super silyl[2i] triflate is



Scheme 1 Plausible mechanism of the silyl Lewis acid-promoted Mukaiyama aldol reaction.

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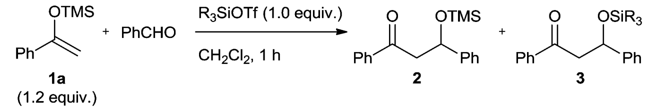
highly effective for the exclusive formation of the Me_3Si aldolate, which proceeds through intramolecular Me_3Si^+ transfer.

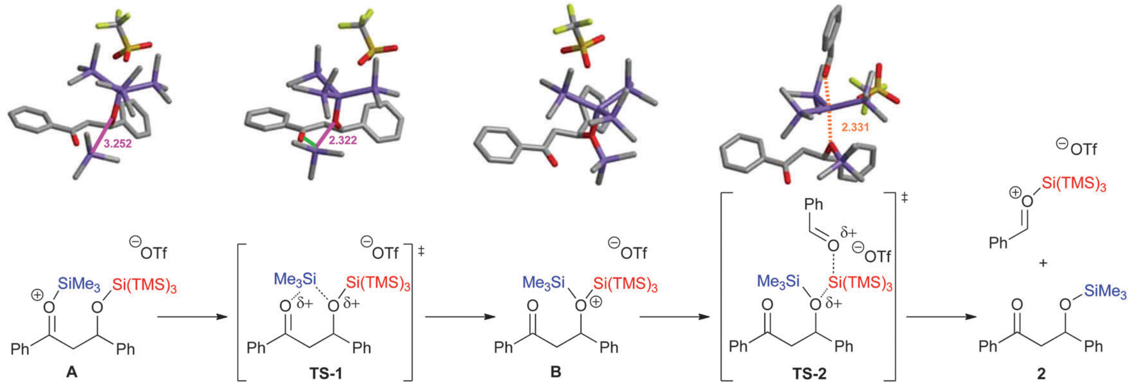
Initially, the Mukaiyama aldol reaction of benzaldehyde with Me_3Si silyl enol ether of acetophenone **1a** was carried out in the presence of a stoichiometric amount of silyl triflate (R_3SiOTf) (Table 1). R_3SiOTf was preformed by the reaction of allylsilane with trifluoromethanesulfonic acid, which completes the protodesilylation at room temperature within 1 h. The use of $^tBuMe_2SiOTf$ as the stoichiometric promoter afforded nearly a 1 : 1 mixture of the Me_3Si aldolate **2** and the $^tBuMe_2Si$ aldolate **3a** at 0 °C (entry 1). Even at −78 °C, poor chemoselectivity was observed (entry 2). A considerable improvement in chemoselectivity was obtained when $^tBuMe_2SiOTf$ was replaced by bulkier $^iPr_3SiOTf$ (entries 3 and 4). Intriguingly, the use of super silyl triflates such as $(TMS)_3SiOTf$ and $(TES)_3SiOTf$ resulted in a marked change in chemoselectivity, leading to the exclusive formation of **2** (entries 6–8).

Table 1 Screening of silyl Lewis acids in the Mukaiyama aldol reaction[a]

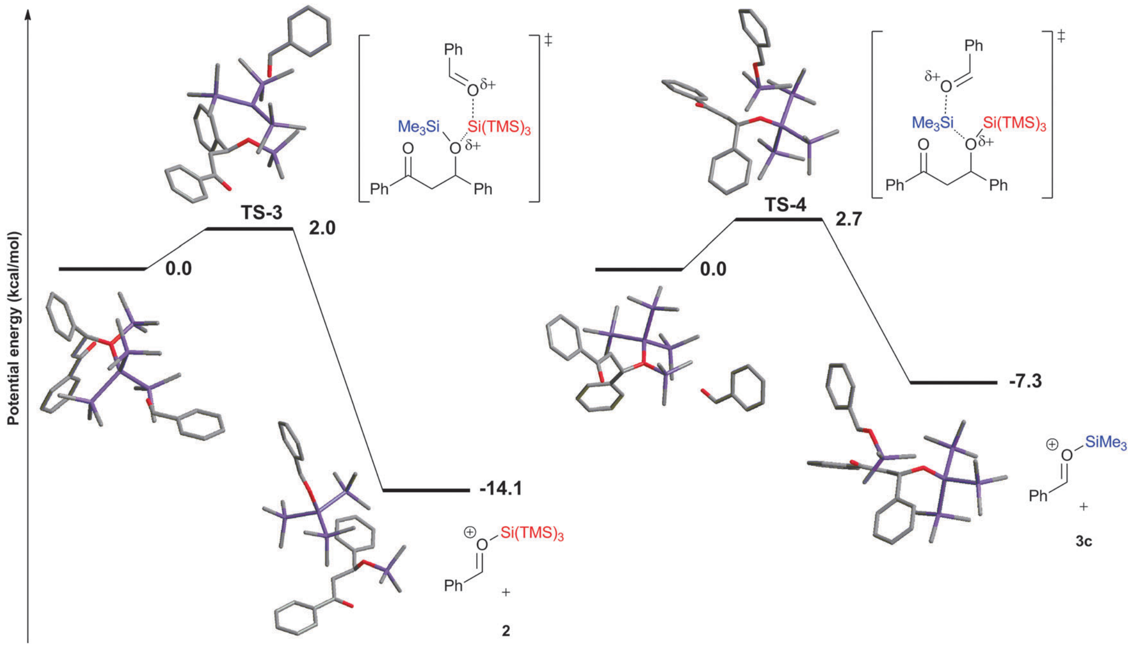


Entry	R_3Si	Temp. (°C)	Yield[b] (%) 2	Yield[b] (%) 3	2/3
1	TBS	0	50	46 (**3a**)	1.1 : 1
2	TBS	−78	71	27 (**3a**)	2.7 : 1
3	TIPS	0	71	25 (**3b**)	2.9 : 1
4	TIPS	−78	86	10 (**3b**)	8.6 : 1
5	$(TMS)_3Si$	0	91	2 (**3c**)	45 : 1
6	$(TMS)_3Si$	−78	95	0 (**3c**)	2 only
7	$(TES)_3Si$	0	82	0 (**3d**)	2 only
8	$(TES)_3Si$	−78	94	0 (**3d**)	2 only

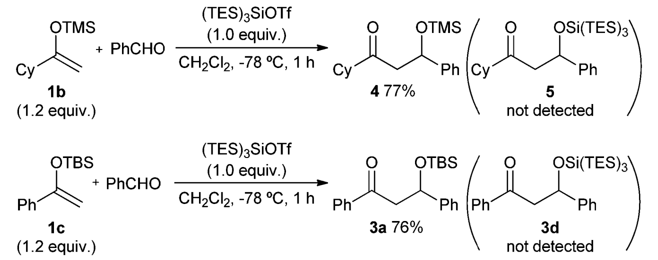
[a] Reaction conditions: **1a** (0.60 mmol), benzaldehyde (0.50 mmol), silyl triflate (0.50 mmol), CH_2Cl_2 (3.0 ml), 1 h. [b] Determined by ^1H NMR analysis of the crude reaction mixture.



Scheme 2 Mechanistic study on the chemoselective silyl transfer in the $(TMS)_3SiOTf$-promoted Mukaiyama aldol reaction.



Scheme 3 Potential energy profiles for the addition of benzaldehyde to $(TMS)_3Si^+$ and Me_3Si^+.



Scheme 4 Chemoselective silyl transfer in the (TES)$_3$SiOTf-promoted Mukaiyama aldol reaction.

To gain mechanistic insight into the perfect chemoselectivity observed when using super silyl triflates, density functional theory (DFT) calculations have been performed with M06-2X functionals (Scheme 2).[12] The reaction of benzaldehyde with **1a** using (TMS)$_3$SiOTf as the promoter affords the intermediate **A**. **A** has accessible intramolecular interaction of the alkoxy oxygen atom with Me$_3$Si$^+$, which triggers the Me$_3$Si$^+$ transfer. The distance of the newly formed Si–O bond ranges from 3.252 Å in **A** to 2.322 Å in **TS-1**, reflecting the silicon-bridged transition structure, which leads to the intermediate **B**. Then, addition of another benzaldehyde to the bulkier (TMS)$_3$Si$^+$ selectively occurs (**TS-2**), providing **2** as the exclusive product. In order to obtain more accurate information on **TS-2**, potential energy profiles for the addition of benzaldehyde to (TMS)$_3$Si$^+$ (**TS-3**) and Me$_3$Si$^+$ (**TS-4**) were respectively calculated (Scheme 3). The calculated activation energy in **TS-3** (2.0 kcal mol^{-1}) was less than that in **TS-4** (2.7 kcal mol^{-1}), indicating that addition of benzaldehyde to (TMS)$_3$Si$^+$ would be energetically more favored than that to Me$_3$Si$^+$.[13] Relief of steric congestion around the alkoxy oxygen atom would provide a lower activation barrier in **TS-3**.[14]

The chemoselective silyl transfer in the super silyl triflate-promoted Mukaiyama aldol reaction was applied to other substrates (Scheme 4). In the case of Me$_3$Si silyl enol ether of cyclohexyl methyl ketone **1b**, only the Me$_3$Si aldolate **4** was produced. We also carried out the reaction of benzaldehyde with ^{t}BuMe$_2$Si-protected silyl enol ether of acetophenone **1c**. The reaction proceeded through intramolecular ^{t}BuMe$_2$Si$^+$ transfer, giving **3a** as the exclusive product. In both cases, none of the (TES)$_3$Si aldolate was observed by ^{1}H NMR analysis of the crude reaction mixture.

In conclusion, we have investigated the influence of the silyl group of the silyl triflates on the chemoselective silyl transfer in the Mukaiyama aldol reaction. As a result, we demonstrated that perfect chemoselective silyl transfer could be realized when super silyl triflates were used as the promoters; the Me$_3$Si group of Me$_3$Si silyl enol ether chemoselectively transferred to the aldolate product and the super silyl group of super silyl triflate did not remain in the product. To gain insight into the perfect chemoselectivity of the reaction, DFT calculations have been performed. These findings provide a basis for future research on designing new chiral silyl Lewis acid catalysts and their use for the asymmetric Mukaiyama aldol reaction.

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