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Aromatic Aldehyde-Selective Aldol Addition with Aldehyde-Derived Silyl Enol Ethers

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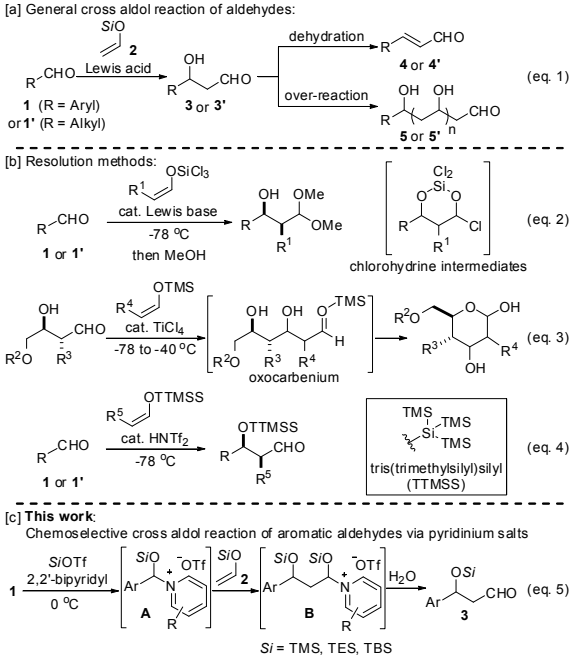
The aldol reaction using aldehyde-derived silyl enolates as nucleophiles with aromatic aldehydes chemoselectively proceeded in the presence of silyl triflate and 2,2'-bipyridyl to produce *β*-siloxy aldehydes, while the aliphatic aldehydes were completely recovered. The unprecedented chemoselectivities depend on the reactivities of the pyridinium-type intermediates derived from the aromatic and aliphatic aldehydes.

Carbon-carbon bond formations represented by the aldol reaction are fundamental and important in organic synthesis.[1] The cross-aldol reaction among different carbonyl substrates can be traditionally accomplished by the preliminary formation of a particular carbonyl substrate into the corresponding enolate as a nucleophile to avoid the undesired self-condensation.[2] The Mukaiyama aldol reaction using silyl enol ethers as easily-handled nucleophiles is well-known to be a powerful and practical synthetic tool,[3] while the cross aldol reaction of an aldehyde (**1** or **1'**) with silyl enol ethers derived from acetaldehydes (**2**) as a nucleophile is still challenging (eq. 1). Namely, **1**/**1'** and **2** can be coupled in the presence of a Lewis acid to give the *β*-hydroxy aldehydes (**3** or **3'**), which comparatively easily undergo the dehydration to form undesired *α*,*β*-unsaturated aldehydes (**4** or **4'**). Furthermore, the generated aldehydes (**3**/**3'** and **4**/**4'**) are also reactive and the suppression control of the oligomerization to the oligomers (e.g., **5** or **5'**) by the addition of the remaining **2** is generally difficult.[4] The reaction of an aldehyde (**1** or **1'**) using trichlorosilyl enol ether gave the proposed chlorohydrine intermediates to avoid the over-reaction, and the following addition of MeOH provided the corresponding acetal (eq. 2).[5] The in *situ*-generated aldehyde resulting from the aldol reaction between the *β*-hydroxy aldehyde as the starting material and the trimethylsilyl enol ether could be trapped as a hemiacetal by the intramolecular nucleophilic attack of the hydroxy group to give the carbohydrate (eq. 3).[6] Furthermore, the use of tris(trimethylsilyl)silyl (TTMSS) enol ethers possessing a bulky silyl moiety could also solve the problematic over-reaction to produce the *β*-siloxy aldehyde derivatives, which easily underwent further chemical modifications (eq. 4).[7] In addition, organocatalytic aldol reactions[8] and asymmetric aldol reactions using boron enol ethers[9] have been reported. However, there are no reports accomplishing the chemoselectivity between the aromatic and aliphatic aldehydes. We now demonstrate the aromatic aldehyde (**1**: Ar-CHO)-selective Mukaiyama aldol reaction with the silyl enol ether as a nucleophile in the presence of the silyl triflate and a pyridine derivative via two kinds of pyridinium salt intermediates (**A** and **B**) (eq. 5), and the further modifications of the obtained *β*-siloxy aldehydes (**3**) were carried out.



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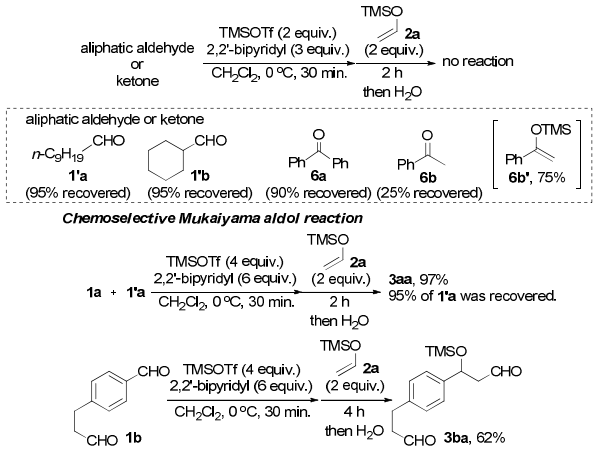
We initially investigated the aldol reaction between 4-methoxybenzaldehyde (**1a**) and trimethylsilyl (TMS) enol ether (**2a**) derived from acetaldehyde in CH_2Cl_2 at 0 °C (Table 1). The use of 2 equiv. of trimethylsilyl triflate (TMSOTf) as a Lewis acid gave a complex mixture including the undesired 4-methoxycinnamaldehyde (**4aa**; 48%), unchanged **1a** (6%) and unidentified oligomers like **5**, and the desired *β*-siloxy aldehyde (**3aa**) was never detected (entry 1). The reaction under basic conditions in the presence of an excess amount (3 equiv.) of pyridine derivatives together with TMSOTf was next examined. While pyridine, *N*,*N*-dimethyl-4-aminopyridine (DMAP) and 2-picoline rather interfered with the reaction progress (entries 2-4), 2,6-lutidine and 2,4,6-collidine gave the desired **3aa** in the moderate yields (57 and 45%, respectively; entries 5 and 6). 2-Phenylpyridine and 2,2'-bipyridyl were much better additives to give **3aa** in excellent yields (entries 7 and 8), while 2,4'-bipyridyl was totally ineffective (entry 9). The detailed optimization results of the solvent, TMSOTf/2,2'-bipyridyl ratio, Lewis acid and base are described in the Electronic Supplementary Information (ESI).

Meanwhile, aliphatic aldehydes (**1'a** and **1'b**) and benzophenone (**6a**) were inert under the above reaction conditions in the presence of TMSOTf and 2,2'-bipyridyl, and the starting compounds were completely recovered (Scheme 1, top). [The reaction of acetophenone (**6b**) as a substrate gave 75% of silyl enol ether (**6b'**) together with 25% of recovered **6b**.] Therefore, the aromatic aldehyde-selective aldol reaction coexisting with aliphatic aldehydes has been accomplished. When using a 1:1 mixture of **1a** and **1'a** as substrates, **1a** was chemoselectively transformed into **3aa** in 97% yield and **1'a**

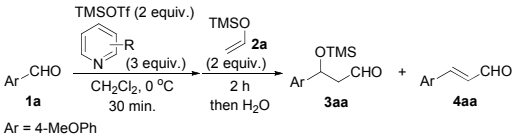


Scheme 1. Chemoselective Mukaiyama aldol reaction.

remained unchanged (Scheme 1, middle). The present chemoselectivity could be achieved by the use of triethylsilyl enol ether and *tert*-butyldimethylsilyl enol ether as other silyl enolates (See ESI). Furthermore, the substrate (**1b**) bearing aromatic and aliphatic aldehydes within the same molecule was also converted into the corresponding *β*-siloxy aldehyde (**3ba**) resulting from the chemoselective transformation of the aromatic aldehyde (Scheme 1d, bottom).

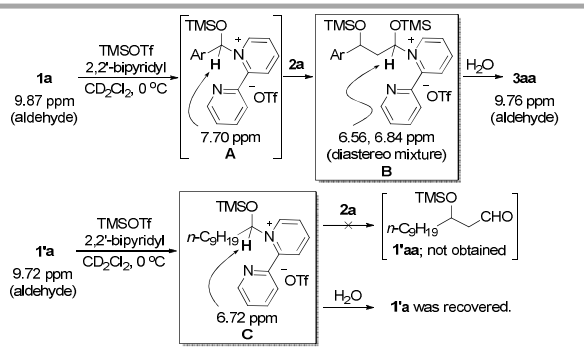
The reaction mechanism was proposed based on NMR studies (Spectra are indicated in ESI). The formation of the pyridinium salt intermediate bearing an *N*,*O*-acetal structure from an acetal in the presence of silyl triflate (*Si*OTf) via the nucleophilic substitution of an alkoxy group of the acetal by a pyridine derivative has been reported.[10] The pyridinium salt intermediate possesses an electrophilicity and reacts with various nucleophiles. In a similar way, both aromatic and aliphatic aldehydes can be transformed into the corresponding pyridinium salt (*N*,*O*-acetal) intermediates (**A** and **C**) by the nucleophilic attack of 2,2'-bipyridyl on the activated aldehyde by TMSOTf (Scheme 2). The proton peaks of each aldehyde [9.87 (**1a**) and 9.72 (**1'a**) ppm] disappeared and the novel characteristic peaks corresponding to each *N*,*O*-acetal [7.70 (**A**) and 6.72 (**C**) ppm] developed. Furthermore, **A** was chemoselectively converted into a diastereomixture of the*β*-siloxy aldehydes (**3ca**-**3ma**). Benzyl and silyl ethers as protected hydroxyl groups (**1h** and **1i**) could be tolerated the intermediates **B** (6.58/6.84 ppm for each of the *N*,*O*-acetal isomers) in the presence of **2a**, which was worked up with H_2O

Table 1. Effect of additional pyridine derivatives.



entry	pyridine derivative	yield [%][a]		
		1a	**3aa**	**4aa**
1	—	6	0	48
2	pyridine	98	0	0
3	DMAP	99	0	0
4	2-picoline	97	1	0
5	2,6-lutidine	40	57	0
6	2,4,6-collidine	46	45	0
7	2-phenylpyridine	2	94	0
8	2,2'-bipyridyl	4	96(90[b])	0
9	2,4'-bipyridyl	90	0	0

[a] The yield was determined by ^{1}H NMR using 1,2-methylenedioxybenzene as an internal standard. [b] Isolated yield.



Scheme 2. ^{1}H NMR studies of the reaction intermediates. (Spectra of **A**, **B** and **C** are included in the ESI.)

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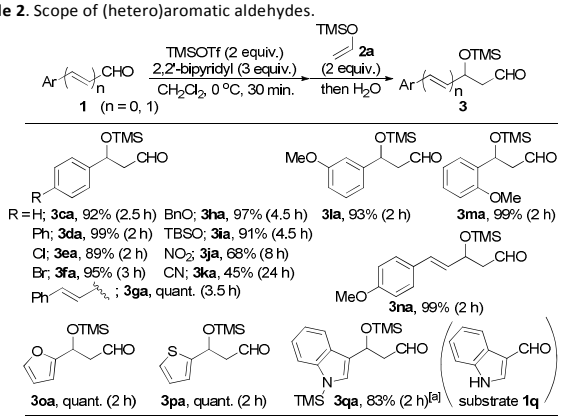
Table 2. Scope of (hetero)aromatic aldehydes.



[a] The reaction was performed using 2,2′-bipyridyl (6 equiv.) and TMSOTf (4 equiv.).

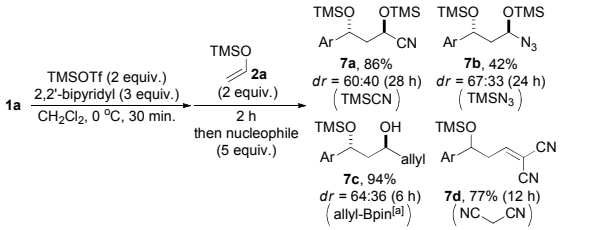
to give the desired **3aa** (9.76 ppm for the aldehyde peak). The results shown in Table 1 indicated that the effect of steric hindrance around the nitrogen atom of the pyridine derivative is quite important to facilitate the present reaction. For example, the pyridinium salt intermediate (**A**) might be more reactive toward the nucleophilic attack of **2a** based on the higher leaving-group ability of the pyridinium moiety bonded to the benzylic carbon in comparison to the non-benzylic **B** and **C**. Furthermore, the steric repulsion by both aromatic rings derived from the starting aldehyde (**1a**, Ar) and the relatively bulky substituent (the pyridine ring of 2,2′-bipyridyl) at the 2-position of the pyridine ring also encourage the reaction progress. Therefore, the undesired over-reaction of **B** with **2a** could be preferentially suppressed.

Various aromatic aldehydes (**1**) were applicable for the reaction with **2a** (Table 2). Benzaldehyde derivatives bearing electron donating and withdrawing groups on the aromatic ring (**1c**-**1m**) were efficiently converted to the corresponding stated reaction conditions. Furthermore, cinnamaldehyde (**1n**) and hetero aromatic aldehyde derivatives (**1o**, **1p** and **1q**) were also applicable to give the corresponding *β*-siloxy aldehydes in excellent yields.

Various silyl enol ethers derived from aliphatic aldehydes were next investigated as nucleophiles of the reaction with **1a** in the presence of the corresponding *Si*OTf (Table 3). Triethylsilyl (TES) and *tert*-buthyldimethylsilyl (TBS) enol ethers (**2b** and **2c**) generated from acetaldehyde or cyclohexylaldehyde (**2d**) were applicable to give the corresponding *β*-siloxy aldehydes (**3ab**-**3ad**). The use of *β*–substituted (*Z*)-silyl enol ethers (**2e**-**2i**) gave *α*-substituted *β*-siloxy aldehydes (**3ae**-**3ai**) in high yields and moderate *anti*-selectivities. On the other hand, the *syn*-adduct (**3ag'**) was obtained as the main isomer from the (*E*)-silyl enol ether (**2g'**). 1-Siloxy-1,3-diene (**2j**) could also be used as a nucleophile to give the *δ*-siloxy *α*,*β*-unsaturated aldehyde (**3aj**) in 71% yield.

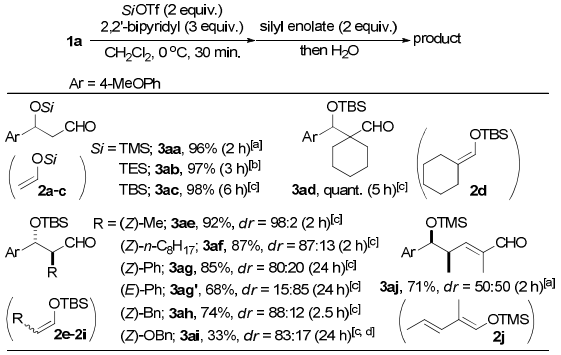
The pyridinium salt intermediate **B** (Scheme 2) via the nucleophilic attack by **2a** could be applicable for further chemical modification in a one-pot manner (Scheme 3). The continuous addition of TMSCN, $TMSN_3$ or allyl-Bpin into the reaction mixture gave the corresponding 1,3-diol derivatives (**7a**, **7b** and **7c**) in moderate to excellent yields.[11] Furthermore, the 1,1-dicyano alkene product (**7d**) could be obtained in 77% yield by the use of malononitrile via the nucleophilic attack and subsequent dehydration. Based on these reactions, the four components (**1a**, **2a**, TMS group of TMSOTf and the corresponding nucleophile) could be continuously condensed to construct highly functionalized compounds in a one-pot approach.

The four-component condensation reaction could also be accomplished using benzaldehyde dimethyl acetal (**8**) instead of aromatic aldehydes (Scheme 4, top). **8** was treated with TMSOTf and 2,2′-bipyridyl in CH_2Cl_2 at 0 °C, and TES enol ether (**2b**) and TMSCN were sequentially added to the reaction mixture. Consequently, the TMS-protected alcohol (**9**) was obtained as the sole product. During the transformation of **A** derived from an aromatic aldehyde (**1**) into **B**, two possible

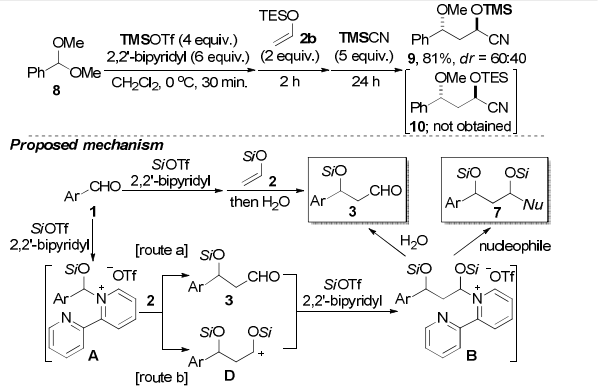


Scheme 3. One-pot four component condensation. [a] 2 equiv. of allyl-Bpin was used.

Table 3. Scope of silyl enolates.



[a] TMSOTf was used. [b] TESOTf was used. [c] TBSOTf was used. [d] 59% of **1a** was recovered.



Scheme 4. Proposed reaction mechanism for the reaction between aromatic aldehydes (**1**) and silyl enolates (**2**) via two kinds of pyridinium salts (**A** and **B**).

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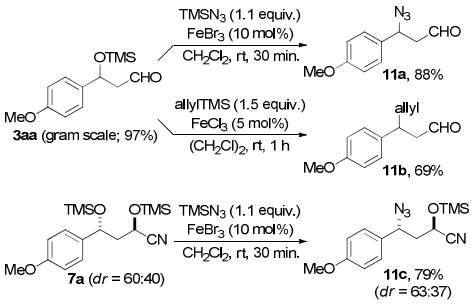

Scheme 5. Further chemoselective transformation of the obtained benzyl silyl ethers.

reaction paths via a *β*-siloxy aldehyde (**3**; route **a**) and a carbocation intermediate (**D**; route **b**) are proposed. If the reaction proceeds through **D**, the corresponding TES-protected alcohol (**10**) should be obtained by the reaction of **8** using the TES-derived silyl enol ether (**2b**). Because we have never detected **10** in the reaction mixture, route **a** might be the probable pathway. In the present reaction using an aromatic aldehyde as the substrate, the product **3** could be produced as a short-lived intermediate in the reaction media and instantaneously masked (protected) by the *Si*OTf and 2,2'-bipyridyl to give **B** without any over-reaction with **2**.

The products, obtained by the present reaction, possesses the benzyl silyl ether moiety within the molecule, which was easily and chemoselectively activated by $FeCl_3$ or $FeBr_3$.[12] The siloxy moiety of **3aa** could be transformed by iron-catalyzed nucleophilic substitutions in the presence of $TMSN_3$ or allylTMS to give the corresponding products (**11a** and **11b**) in good yields (Scheme 5). **7a** bearing two kinds of siloxy functionalities was chemoselectively converted by the treatment with $TMSN_3$ to the azido product (**11c**) via the $FeBr_3$-catalyzed chemoselective transformation of only the benzylic siloxy moiety.

In conclusion, we have developed the aromatic aldehyde-selective aldol reaction using silyl enol ethers derived from aliphatic aldehydes via two kinds of pyridinium salt intermediates. The different electrophilicities between the aromatic and aliphatic pyridinium salts intermediates enable the suppression of the over-reaction. The obtained reaction intermediates and products could be continuously and easily modified into the highly-functionalized compounds. The unprecedented and chemoselective transformations are useful to develop a novel strategy for synthesis of the target molecules.

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Conflicts of interest

There are no conflicts to declare.

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