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Chemoselective Two-Directional Reaction of Bifunctionalized Substrates: Formal Ketal-Selective Mukaiyama Aldol Type Reaction

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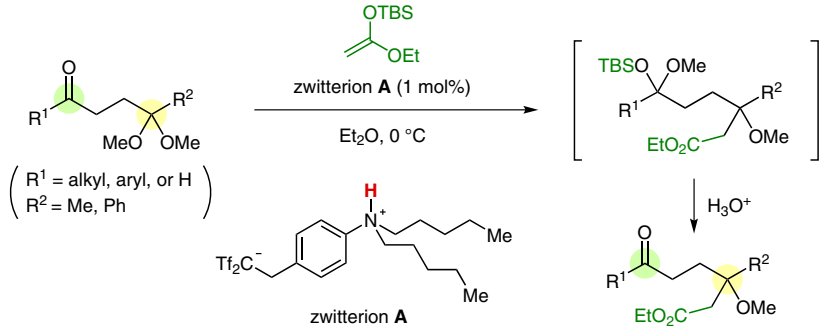

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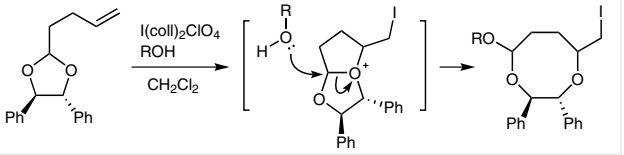
Abstract In the presence of an acidic zwitterion bearing a highly stabilized carbanion, reactions of ω,ω-dialkoxy carbonyl compounds with ketene silyl acetals (KSA) resulted in an unusual molecular transformation; substitution reaction with the KSA at the ketal moiety and simultaneous silylative acetalization of the ketone moiety.

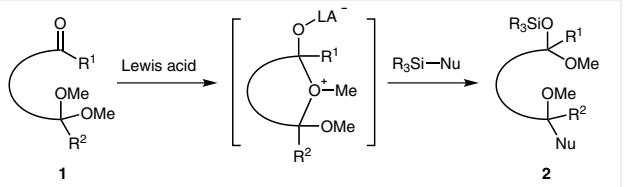
Key words acid catalysis, zwitterion, carbanion, chemoselectivity, Mukaiyama aldol reaction

Chemoselective molecular transformations of multifunctionalized substrates bearing two or more reactive groups are key methodologies for organic synthesis. From the viewpoints of atom and step economies, the numbers of protection/deprotection steps should be as small as possible in chemical synthesis.[1] Such requirement in organic synthesis encourages highly chemoselective reactions. An alternative strategy in order to increase the efficiency of synthesis would be the two-directional synthesis using symmetric or pseudosymmetric bifunctionalized substrates.[2] We were interested in a combination of the chemoselectivity and the two-directional strategy, in other words, the highly chemoselective C–C bond-forming reaction at one reactive group of the substrates along with simultaneous transformation of another reactive group.

As an informative example, Kita and Fujioka reported a reaction of alkenyl acetals with iodonium sources in the presence of alcohols as nucleophiles (Scheme 1).[3] They proposed that the intramolecular iodoetherification-type reaction giving rise to the bicyclic oxonium and the following alcoholysis proceeded to give the ring-expanded product. This inspired us to study the transformation of ω,ω-dialkoxy ketones **1**, which had the polar carbonyl group instead of the alkene structure, using carbon nucleophiles (Scheme 2).



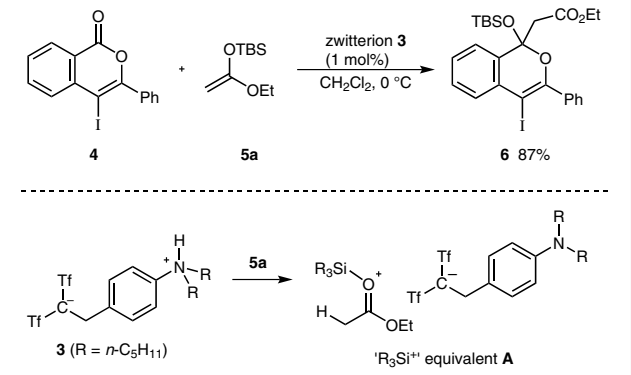
Scheme 1 Reaction of alkenyl acetals with iodonium sources



Scheme 2 This work

Here some difficulties were easily predictable in our case. First, chemoselective activation of the carbonyl group over the ketal functionality would be required. However, the use of typical Lewis acids was at risk to activate not only the carbonyl but also the ketal without the selectivity. For instance, in a typical Mukaiyama aldol reaction, both carbonyl and ketal substrates served as good substrates.[4,5] For this issue, a number of researches revealed that well-considered choice of the Lewis acid promoters brought about carbonyl-selective activation.[6] The second point was the background reaction with the nucleophiles at the initially activated carbonyl group. To overcome these problems, we focused on the zwitterion-induced addition reaction of ketene silyl acetals (KSA) to lactone substrates.[7] Recently, we reported that acidic zwitterion **3**[8] nicely promoted the addition reaction of KSA **5a** to isocoumarin **4**

to give the corresponding silyl acetal **6** without decomposition of some acid-sensitive functionalities including pyrane and silyl acetal moieties in the product (Scheme 3). In this reaction system, in situ generation of loosely contacting ion pair **A** as a catalytically active species was assumed.[9]

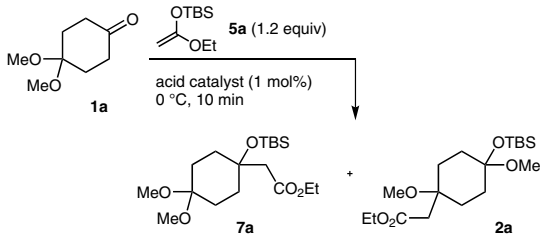


Scheme 3 Zwitterion-induced addition reaction of KSA to lactones

That is, this species worked as a highly Lewis acidic formal 'R_3Si^+'equivalent to activate **4** through the silyl transfer reaction from **A** to the carbonyl group of **4**.[10] Our observation suggested that, under the zwitterion-mediated conditions, the desired selective activation of the carbonyl group over the ketal functionality in substrate **1** would be possible. In this paper, we describe the chemoselective two-directional reaction of the ω,ω-dialkoxy ketones under the zwitterion-induced conditions. This reaction realized the unusual ketal-selective Mukaiyama aldol type reaction[11] along with the protection of the substrate carbonyl group by a single reaction operation.

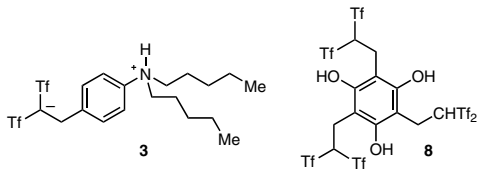
At first, we examined the reaction of 4,4-dimethoxycyclohexanone (**1a**) with KSA **5a**. The selected results are summarized in Table 1. Upon treatment with 1.2 equivalents of **5a** and 1 mol% of zwitterion **3**, the substrate **1a** was rapidly consumed (Table 1, entry 1). After usual extractive workup followed by chromatographic purification, simple Mukaiyama aldol product **7a** was isolated in 24% yield. The desired methyl silyl ketal **2a** (two diastereomers in a ratio of 3.5:1) was obtained in 61% yield as well. This fact supported our hypothesis. By optimizing the reaction conditions, we successfully found that ethereal solvents such as diethyl ether (Et_2O) and 1,2-dimethoxyethane (DME) were better options to effect the desired reaction (Table 1, entries 2 and 3). For example, the reaction in Et_2O gave **2a** in 94% yield, exclusively. On the other hand, the use of more polar THF did not meet good consumption of **1a**. It should be noted that the present transformation realized the C–C bond formation at the ketal functionality and the protection of the carbonyl group in a single reaction operation. In this reaction system, the use of TfOH and Tf_2NH instead of **3** yielded a complex mixture (Table 1, entries 4 and 5). Carbon acid

Table 1 Reaction of 4,4-Dimethoxycyclohexanone **1a** with KSA **5a**



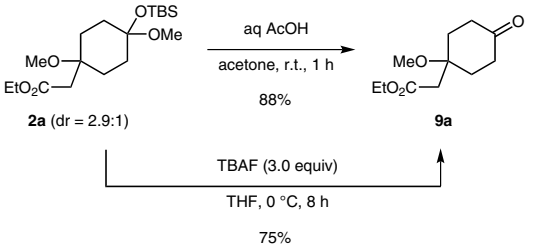
Entry	Acid catalyst	Solvent	Yield of **7a** (%)[a]	Yield of **2a** (%)[a]	dr of **2a**
1[b]	zwitterion **3**[d]	CH_2Cl_2	24	61	3.5:1
2	zwitterion **3**[d]	Et_2O	0	94	2.9:1
3	zwitterion **3**[d]	DME	0	87	3.9:1
4	TfOH	Et_2O	0	0	–
5[c]	Tf_2NH	Et_2O	0	0	–
6[c]	carbon acid **8**[d]	Et_2O	0	34	3.0:1
7	TBSOTf	Et_2O	<5	21	2.1:1
8	4-pyrrolidinylbenzoic acid	Et_2O	0	0	–

[a] Isolated yield.
[b] Reaction was carried out for 1.5 h at –40 °C.
[c] A complex mixture was obtained.
[d]



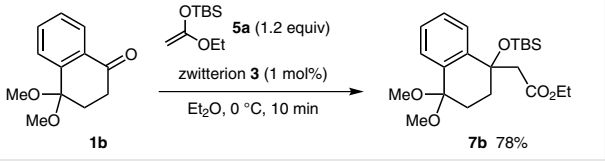
8[12,13] and TBSOTf were also applicable, while the yields of **2a** were dissatisfactory (Table 1, entries 6 and 7). Furthermore, 4-(pyrrolidin-1-yl)benzoic acid was ineffective for this transformation (Table 1, entry 8).

With methyl silyl ketal **2a** in hands, its hydrolysis was studied (Scheme 4).[14] In a mixed solvent of AcOH–H_2O–acetone (1:1:1 v/v), **2a** was easily hydrolyzed to give ketone **9a** in 88% yield. Moreover, the same transformation was achieved by treating **2a** with tetrabutylammonium fluoride (TBAF). Overall chemistry (the zwitterion-induced reaction with KSA followed by ketonization) was equivalent to the unusual ketal-selective Mukaiyama aldol reaction.



Scheme 4 Conversion of silyl acetal **2a** to ketone **9a**

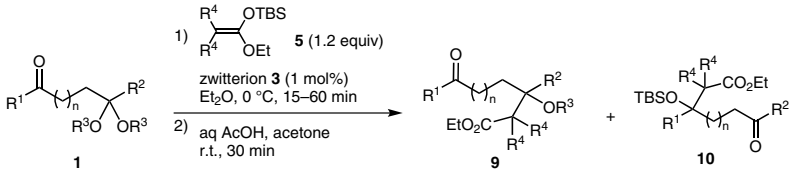
Next, we conducted the reaction of benzene-fused substrate **1b** (Scheme 5). However, in this case, the reaction at the carbonyl group was faster than that at the ketal moiety.[15] This would be ascribable to lower conformational flexibility of the substrates.

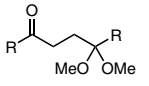
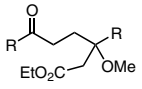
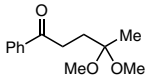
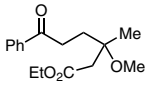
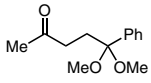
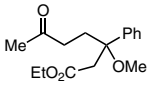
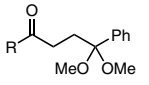
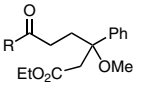
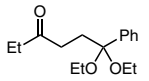
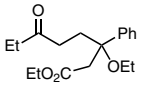
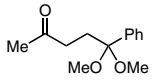
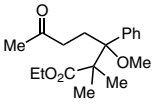
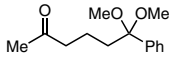
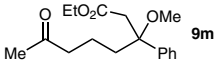


Scheme 5 Reaction of **1b** with **5a**

Indeed, several acyclic substrates gave excellent results under the optimized conditions. Selected results are summarized in Table 2. The reaction of **1c** with KSA **5a** (R = H) yielded the desired methyl silyl ketal in 87% yield (dr = 1:1.0) without formation of any side products. After acidic hydrolysis of thus obtained crude material in a one-pot manner, ketone **9c** was isolated in 87% yield from **1c** (Table 2, entry 1). According to this one-pot procedure, the reaction of diphenyl substrate **1d** was also conducted. Although preferential formation of the desired **9d** was observed in the reaction in Et_2O, the chemoselectivity was moderate (Table 2, entry 2). This problem was successfully solved by using DME instead of Et_2O; **9d** and **10d** were isolated in 81%, 3% yields, respectively, after acid hydrolysis (Table 2, entry 3). By the reaction of phenyl ketone **1e** in Et_2O, **9e** was obtained in 69% yield along with formation of a small amount of **10e** (Table 2, entry 4).

Table 2 Reaction of ω,ω-Dialkoxy Carbonyl Compounds **1** with KSA **5**

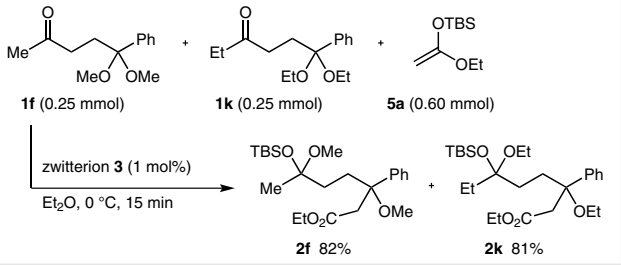


Entry	1		9		Yield of **9** (%)[a]	Yield of **10** (%)
1		**1c** (R = Me)		**9c**	87	–
2		**1d** (R = Ph)		**9d**	58	31
3[b]		**1d**		**9d**	81	3
4		**1e**		**9e**	69	7
5		**1f**		**9f**	83	–
6		**1g** (R = Et)		**9g**	92	–
7		**1h** (R = *i*-Bu)		**9h**	91	–
8		**1i** (R = *c*-C_3H_5)		**9i**	73	18
9		**1j** (R = H)		**9j**	71	–
10		**1k**		**9k**	92	–
11[c]		**1f**		**9f'**	85	–
12[d]		**1m**		**9m**	35	20
13[b,d]					61	15

[a] Isolated yield.
[b] The reaction was carried out by using 1.6 equiv of **5** in DME as a solvent.
[c] 5 mol% of carbon acid **8** were used.
[d] 1-Phenylhexane-1,5-dione was also obtained.

In contrast, methyl ketone **1f**, which differed from **1e** in the positions of phenyl and methyl groups, specifically produced **9f** in 83% yield (Table 2, entry 5). Under similar conditions, ethyl ketone **1g** and isobutyl ketone **1h** gave selectively **9g** and **9h** in excellent yields (Table 2, entries 6 and 7). The reaction of cyclopropyl ketone **1i** remained to proceed in a ketal-selective manner, and **9i** was isolated in 73% yield (Table 2, entry 8). Surprisingly, aldehyde **1j** was also converted into **9j** in 71% yield (Table 2, entry 9). Diethyl ketal **1k** could be used as a suitable substrate (Table 2, entry 10). When the reaction of **1f** with disubstituted KSA **5b** (R = Me) was addressed in the presence of zwitterion **3**, no reaction was observed. However, by using stronger acid **8** instead of **3**, the desired product **9f'** was obtained in 85% yield (Table 2, entry 11). Although the reaction of δ,δ-dimethoxy ketone **1m** with **5a** in Et_2O gave **9m** in 35% yield due to the competitive formation of **10m**, the reaction in DME gave **9m** in an acceptable yield (Table 2, entries 12 and 13).

To gain insights into the reaction pathway, we also conducted a crossover study; the reaction using an equimolar mixture of **1f** and **1k** (Scheme 6).



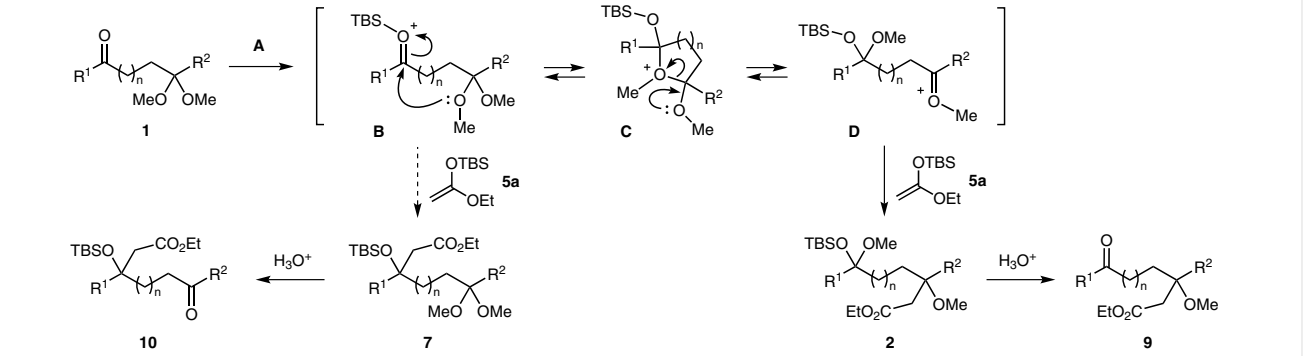
Scheme 6 Crossover study using **1f** and **1k**

When this mixture was treated with KSA **5a** (**1f**, 0.25 mmol; **1k**, 0.25 mmol; **5a** 0.60 mmol) in the presence of 1 mol% of **3**, two silyl acetals **2f** and **2k** were isolated in 82% and 81% yields, respectively. Indeed, no scrambling of the alkoxy groups was observed in this reaction. The present result implied that, in each substrate, the 1,4-migrations of the alkoxy group during the reaction strictly occurred in an intramolecular manner.

On the basis of observed chemoselectivity and the crossover study, we propose a reaction pathway as shown in Scheme 7. At first, the in situ generated 'R_3Si^+' equivalent **A** reacts with the ketone moiety of **1** to give silyl carboxonium **B**. In cases of conformationally flexible substrates, **B** is smoothly captured by the methoxy group in an intramolecular manner (formation of **C**). The following ring opening giving rise to **D** causes the 1,4- or 1,5-migration of the methoxy group. In such reaction system, the site-selectivity of nucleophilic attack by KSA would reflect thermodynamic distribution between **B** and **D**. As mentioned above, ethereal solvents such as Et_2O and DME were effective to obtain **2**. This suggested that stabilization of the cationic intermediates **B** and **D** by solvation played an important role.

Compared with the silyl carboxonium **B** equipped with sterically bulky TBS group near the cationic center, less hindered methyl carboxonium **D** would be strongly stabilized by effective solvation.[16] In fact, the reaction outcomes of a pair of substrates **1e** (R^1 = Ph, R^2 = Me) and **1f** (R^1 = Me, R^2 = Ph) also supported these cationic intermediates; phenyl ketone **1e** gave a mixture of **9e** and **10e**, whereas, methyl ketone **1f** produced **9f** in a one-sided manner. In the former, since the silyl carboxonium **B** (R^1 = Ph, R^2 = Me) was exceptionally stabilized by the resonance effect of the phenyl group, a small amount of **10e** was formed.

In summary, we successfully developed a novel chemoselective Mukaiyama aldol type reaction of ω,ω-dialkoxy ketones.[17] From two points of view, the present transformation has advantages. First, this is an example of the unusual ketal-selective Mukaiyama aldol type reaction. Second, the present reaction realized the C–C bond formation to construct the molecular architecture and simultaneous protection of ketone functionality in a single reaction operation.



Scheme 7 Possible reaction pathway for the present reaction

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560478.

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(13) Other examples on carbon acid catalysis, see: (a) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2001**, *40*, 4077. (b) Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 3175. (c) Saadi, J.; Akakura, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 14248.

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(15) Under similar conditions, perfect carbonyl selectivity was observed in the Mukaiuyama aldol reaction of benzaldehyde and its dimethyl acetal with **5a**. Likewise, the reaction of 1,4-dioxaspiro[4.5]decan-8-one, which was a cyclic ketal derivative of **1a**, proceeded in a carbonyl selective manner.

(16) By ^{13}C NMR study, it was indicated that silyl carboxonium was higher electrophilic compared with methylated one, see: Olah, G. A.; Wang, Q.; Li, X.; Rasul, G.; Prakash, G. K. S. *Macromolecules* **1996**, *29*, 1857.

(17) **Typical Procedure (Table 2, Entry 1)**
To a solution of 5,5-dimethoxyhexan-2-one (**1c**, 80.1 mg, 0.501 mmol) and zwitterion **3** (2.6 mg, 5.0 μmol) in Et_2O (1.5 mL) was added a solution of *tert*-butyl[(1-ethoxyvinyl)oxy]dimethylsilane (**5a**, 121 mg, 0.598 mmol) in Et_2O (0.5 mL) at 0 °C. After being stirred for 20 min at 0 °C, the reaction was quenched by treatment with Et_3N (0.3 mL), then it was concentrated under reduced pressure. The resulting residue was dissolved in a mixed solvent of acetone, H_2O, and AcOH (1:1:1 v/v, 3.0 mL). This mixture was stirred for 30 min at r.t. After usual extractive workup, the obtained residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give ethyl 3-methoxy-3-methyl-6-oxoheptanoate (**9c**) in 87% yield (94.1 mg, 0.436 mmol); colorless oil. IR (neat): ν = 2980, 2947, 2910, 1728, 1717, 1365, 1182, 1075, 1034 cm^{-1}. ^1H NMR (400 MHz, CD_3CN): δ = 1.19 (3 H, t, *J* = 7.2 Hz), 1.19 (3 H, s), 1.71–1.85 (2 H, m), 2.08 (3 H, s), 2.41 (1 H, d, *J* = 13.7 Hz), 2.46 (2 H, t, *J* = 8.0 Hz), 2.47 (1 H, d, *J* = 13.7 Hz), 3.11 (3 H, s), 4.06 (2 H, q, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, CD_3CN): δ = 13.5, 22.1, 29.1, 31.0, 37.3, 42.5, 48.6, 60.0, 74.9, 170.5, 208.2. MS (ESI-TOF): *m/z* = 239 $[M + Na]^+$. HRMS: *m/z* calcd for $C_{11}H_{20}O_4$ $[M + Na]^+$: 239.1259; found: 239.1259. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.91; H, 9.29.