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Mixed Monosilyl Acetals and Catalyst-Dependent Chemoselective Mukaiyama Aldol Reactions

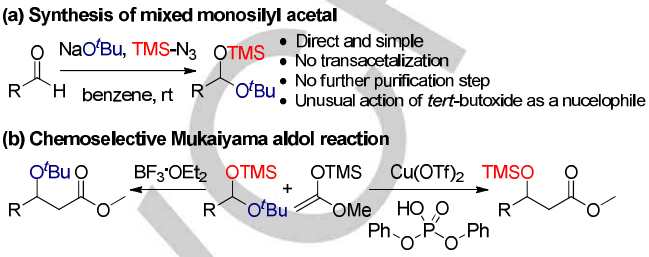
Sun Min Kim,[†][a] Hye Sung Yang,[†][a] Heesung Eum,[b] Hyun-Joon Ha,*[b] and Jung Woon Yang*[a]

Abstract: We report a direct, simple, and straightforward approach for the construction of a mixed monosilyl acetal as a new and synthetically valuable functional group by mixing an aldehyde, sodium *tert*-butoxide and trimethylsilyl azide. We also demonstrate catalyst-dependent chemoselective reaction between mixed monosilyl acetals and silyl ketene acetals through Mukaiyama aldol reactions to give different structures of *O*-protected *β*-hydroxy esters in excellent yields with high chemoselectivities. This study provided the existence of an oxonium ion intermediate and of its kinetically controlled reaction with the pre-equilibrated silyl enol ether obtained from (*E*)- and (*Z*)-isomerization.

O,*O*-Mixed acetals are well-documented as synthetic equivalents of aldehydes or esters and are widely used in diverse synthetic organic reactions, such as the Mukaiyama aldol, Diels-Alder, and radical cyclization reactions.[1] Despite their broad application scope, methodologies for the preparation of mixed acetals have been underdeveloped for the following reason: a mixed acetal is formed by the reaction of a symmetrical acetal with an alcohol in the presence of a Lewis acid catalyst; however, this conventional method leads to concomitant transacetalization to produce a mixture of symmetrical and unsymmetrical acetal. In order to overcome the selectivity intrinsic problem, Fujioka, Kita, and co-workers reported the consecutive reaction of symmetrical acetals with 2,4,6-collodine and triethylsilyl triflate (TESOTf), leading to a reactive pyridinium-type salt as a weak electrophile, followed by the addition of an alcohol.[2] Kiyooka's group attempted to synthesize mixed-monosilyl acetals by the reaction of an ester with DIBAL-H, leading to a reactive aluminoxy acetal, and subsequent addition of trimethylsilyl triflate (TMSOTf)–pyridine.[3] Later on, an analogue reaction using TMS–imidazole instead of TMSOTf–pyridine was investigated by Polt et al.[4]

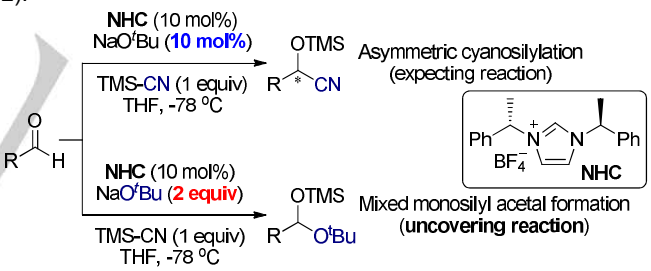
However, the aforementioned methodologies still suffer from indirect approaches, the use of over-stoichiometric amounts of activating agents, and the need of further purifications through distillation or column chromatography providing poor yields.

Herein, we describe a highly selective, direct, and simple operative approach for the synthesis of monosilyl acetals from aldehydes (Scheme 1a). In particular, we demonstrate chemoselective Mukaiyama aldol reactions, relying on the discriminative activation of the alkoxy group on the acetal by different oxophilic catalysts (Scheme 1b).



Scheme 1. (a) Mixed monosilyl acetal formation (b) chemoselective Mukaiyama aldol reactions using mixed monosilyl acetals.

The organic transformation for the synthesis of a mixed monosilyl acetal was discovered during our attempts to synthesize a silylated cyanohydrin product by the reaction of an aldehyde and trimethylsilyl cyanide (TMS–CN) in the presence of 10 mol% of an *N*-heterocyclic carbene (NHC) precatalyst with sodium *tert*-butoxide (NaO^{t}Bu).[5] However, serendipitously, the mixed monosilyl acetal was obtained when the equivalents of NaO^{t}Bu were increased from 0.1 to 2.0, where NaO^{t}Bu served as nucleophile, which is rarely reported in the literature (Scheme 2).[6]



Scheme 2. Unexpected mixed monosilyl acetal formation.

To verify the causes of the unexpected result, we screened different sources of both trimethyl silyl groups and alkoxy groups and the results are summarized in Table 1. We initially examined the reaction of benzaldehyde (**1g**) with NaO^{t}Bu and TMS–Cl in toluene at room temperature for 24 h. However, only a trace amount of product was obtained (Table 1, entry 1). The use of TMS–CN or TMS–N_3 in combination with NaO^{t}Bu produced the desired product in quantitative yields (>99%) (Table 1, entries 2-3). Next, other alkoxy groups like –OMe and –OEt were evaluated, but unfortunately, no product was isolated (Table 1, entries 4–5). On the basis of these observations, we proposed the following reaction mechanism and explanation for the formation of mixed monosilyl acetals: NaO^{t}Bu spontaneously dissociates by intermolecular ion-induced dipole interactions between the sodium cation and the negatively charged terminal nitrogen of the azide, thereby liberating a naked *tert*-butoxide ion with dramatically enhanced nucleophilicity.

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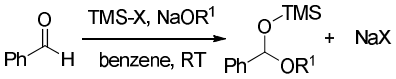
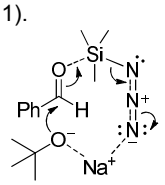
Table 1. Screening of parameters[a]



Entry	TMS–X	$NaOR^1$	Yield [%][b]
1	TMS–Cl	NaO^{t}Bu	trace
2	TMS–CN	NaO^{t}Bu	>99
3	TMS–N_3	NaO^{t}Bu	>99
4	TMS–N_3	NaOMe	N. D.
5	TMS–N_3	NaOEt	trace

[a] General conditions: **1g** (1 mmol), NaOR' (1.2 equiv.) [R = ^{t}Bu (1.0 M solution in THF), R = Me (25 wt% in MeOH), R = Et (21 wt% in EtOH)], TMS–X (1.2 equiv.), benzene (0.5 M), RT. [b] Isolated yield.

Subsequent nucleophilic attack of the *tert*-butoxide anion on the carbonyl carbon of the aldehyde leads to O–Si bond formation and Si–N bond cleavage simultaneously (Scheme 3). Overall, the driving force of this reaction is presumably associated with the strength of ion-dipole interactions [e.g., Na^+---X-TMS (where, X = N_3, CN, or Cl)], which are mainly cause by the dipole moment of TMS-X. The strength of the dipole moment of TMS-X decreases in the following order: TMS-CN [4.38 ± 1.08 D (4.06 D)[7a]] > TMS-N_3 (3.99 ± 1.08 D) >> TMS-Cl [2.80 ± 1.08 D (2.08 D)[7b]],[7] which explains why the reaction with TMS-Cl was sluggish (Table 1, entry 1).



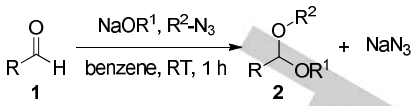
Scheme 3. Plausible mechanism for the formation of mixed monosilyl acetal.

Next, the reaction scope was explored under the optimized conditions. As summarized in Table 2, the reaction proceeded smoothly with a wide range of aromatic aldehydes, *trans*-α,β-unsaturated aldehydes, and aliphatic aldehyde to give the corresponding mixed monosilyl acetals in >99% yields (Table 2, entries 1–13). Different type of silyl source and aliphatic alkoxide are applicable in this study (Table 2, entries 14–15). No desired product was obtained by using NaOPh, but trimethyl(phenoxy)-silane was rendered entirely (Table 2, entry 16) [see Supporting Information]. Notably, mixed monosilyl acetals **2** were isolated from the reaction mixtures without further purification steps like distillation or column chromatography in most cases.

The usefulness of mixed monosilyl acetals would be further elaborated by the addition of a suitable nucleophile to the oxocarbenium intermediates, which are chemoselectively generated by the appropriate choice of oxophilic catalyst, giving structurally different products (Scheme 4).

Thus, we envisioned a chemoselective route to *O*-protected β-hydroxy esters through the Mukaiyama aldol reaction of mixed monosilyl acetal **2** with silyl ketene acetal **3** as nucleophile.

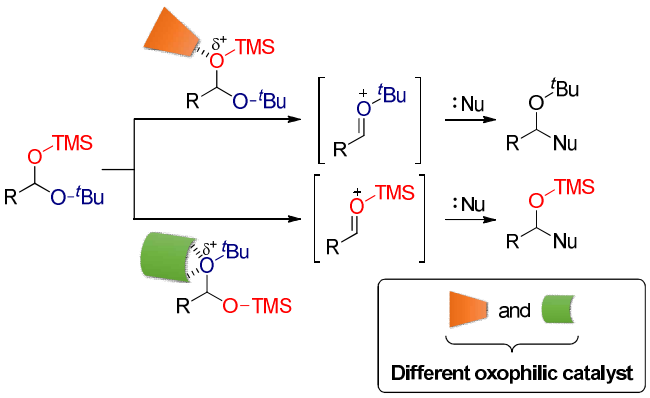
Table 2. Reaction scope for the synthesis of mixed monosilyl acetals[a]



Entry	R	R^1	R^2	Product [yield (%)][b]
1	4-Cl-C_6H_4	^{t}Bu	TMS	**2a** (>99%)
2	3-Cl-C_6H_4	^{t}Bu	TMS	**2b** (>99%)
3	3-Br-C_6H_4	^{t}Bu	TMS	**2c** (>99%)
4	2-Br-C_6H_4	^{t}Bu	TMS	**2d** (>99%)
5	4-CN-C_6H_4	^{t}Bu	TMS	**2e** (>99%)
6	4-Me-C_6H_4	^{t}Bu	TMS	**2f** (>99%)
7	3-Me-C_6H_4	^{t}Bu	TMS	**2g** (>99%)
8	3-MeO-C_6H_4	^{t}Bu	TMS	**2h** (>99%)
9	Ph	^{t}Bu	TMS	**2i** (>99%)
10	2-Naphthyl	^{t}Bu	TMS	**2j** (>99%)
11	C_6H_5CH=CH (*trans*)	^{t}Bu	TMS	**2k** (>99%)
12	C_6H_5CH=C-CH_3 (*trans*)	^{t}Bu	TMS	**2l** (>99%)
13	Cyclohexyl	^{t}Bu	TMS	**2m** (>99%)
14[c]	4-Cl-C_6H_4	^{t}Bu	TBS	**2n** (>99%)
15[d,f]	4-Cl-C_6H_4	^{i}Pr	TMS	**2o** (94%)
16[e]	4-Cl-C_6H_4	Ph	TMS	N.D.

[a] General conditions: **1** (1 mmol), NaO^{t}Bu (1.0 M solution in THF; 1.2 equiv), TMS–N_3 (1.2 equiv), benzene (0.5 M), RT. [b] Isolated yield. TBS = *tert*-butyldimethylsilyl. [c] Using TBS-CN. [d] Using NaO^{i}Pr (2.0 M solution in THF). [e] Using NaOPh (1.0 M solution in THF). [f] Purified by column chromatography on neutral alumina.

For the purpose, we initiated our studies employing oxophilic catalysts for the preferential activation of one of the ethereal oxygen atoms in the mixed acetals.



Scheme 4. The discriminative activation of mixed monosilyl acetals by oxophilic catalysts and chemoselective addition reaction.

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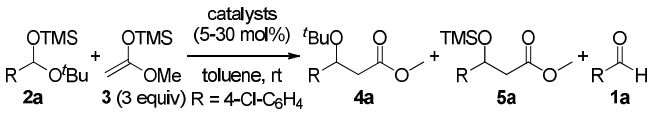
Table 3. Optimization of the chemoselective Mukaiyama aldol reaction[a]



Entry	Catalyst [mol%]	Time [h]	Yields of **4a**:**5a**:**1a** [%][b]
1	$FeCl_3$ (5)	24	4:0:0
2	$AlCl_3$ (5)	24	5:0:0
3	$Zn(OTf)_2$ (5)	24	8:0:0
4	$Cu(OTf)_2$ (5)	24	6:0:0
5	$Yb(OTf)_2$ (5)	24	13:0:14
6	$BF_3{\cdot}OEt_2$ (5)	15	13:0:1
7	$BF_3{\cdot}OEt_2$ (10)	15	20:0:3
8	**$BF_3{\cdot}OEt_2$ (30)**	**1**	**99:0:0**
9	$(C_6H_5O)_2P(O)OH$ (10)	15	0:0:7
10	**$Cu(OTf)_2$-$(C_6H_5O)_2P(O)OH$ (10)**	**12**	**0:84:0**

[a] General conditions: **2a** (0.125 mmol), **3** (0.375 mmol), catalysts (5–30 mol%), toluene [0.0625 M], RT. [b] Isolated yield.

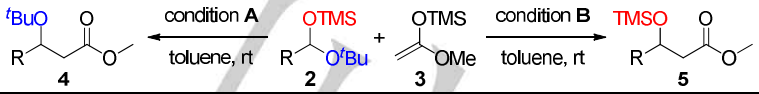
When metal-based Lewis acid catalysts like $FeCl_3$, $AlCl_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, or $Yb(OTf)_2$ were employed, product **4a** was obtained as the major product in low yield (Table 3, entries 1–5). A subtle improvement in both yield and selectivity of **4a** was observed by using boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) as catalyst.

Gratifyingly, the yield and selectivity of **4a** dramatically increased with increasing the catalyst loading from 5 mol% to 30 mol% (Table 3, entries 6–8). Surprisingly, opposite chemoisomer **5a** was observed when a binary catalytic system, such as $Cu(OTf)_2$–Brønsted acid (e.g., diphenylphosphoric acid) was used (Table 3, entry 10).

With these two complementary chemoselective reaction conditions in hand, a variety of monosilyl acetals were reacted with silyl enol ether **3** under individual reaction conditions (Table 4). Most monosilyl acetal aromatic substrates were well tolerated under the optimised conditions regardless of the electronic nature of the aromatic rings (Table 4, entries 1–20). Substrates with an inherent olefin on the R–group provided the corresponding products in moderate–to–high yields (Table 4, entries 21–24)

Based on these observations, we postulated the reaction pathways for the selective formation of ^{t}Bu-/or TMS-protected β-hydroxyester (Scheme 5). $BF_3{\cdot}OEt_2$ coordinates preferably to the –OTMS group than to the –*O-tert*-butyl moiety, whereas the $Cu(OTf)_2$-diphenyl phosphate complex activates the *O-tert*-butyl moiety preferentially, leading to the selective formation of oxocarbenium ions **6** and **7**, respectively.

Table 4. Substrate scope[a]



Condition A					Condition B				
Entry	R	Product	Time	Yield [%][b]	Entry	R	Product	Time	Yield [%][b]
1	4-Cl-C_6H_4	**4a**	30 min	94	2	4-Cl-C_6H_4	**5a**	12 h	84
3	3-Cl-C_6H_4	**4b**	10 min	97	4	3-Cl-C_6H_4	**5b**	5 h	85
5	3-Br-C_6H_4	**4c**	10 min	95	6	3-Br-C_6H_4	**5c**	5 h	86
7	2-Br-C_6H_4	**4d**	10 min	>99	8	2-Br-C_6H_4	**5d**	2 h	90
9	4-CN-C_6H_4	**4e**	10 min	>99	10	4-CN-C_6H_4	**5e**	20 h	35
11	4-Me-C_6H_4	**4f**	10 min	96	12	4-Me-C_6H_4	**5f**	3 h	95
13	3-Me-C_6H_4	**4g**	10 min	96	14	3-Me-C_6H_4	**5g**	3 h	92
15	3-MeO-C_6H_4	**4h**	30 min	94	16	3-MeO-C_6H_4	**5h**	6 h	91
17	Ph	**4i**	10 min	>99	18	Ph	**5i**	6 h	88
19	2-Naphthyl	**4j**	30 min	95	20	2-Naphthyl	**5j**	20 h	67
21	C_6H_5CH=CH (*trans*)	**4k**	2 h	45	22	C_6H_5CH=CH (*trans*)	**5k**	6 h	70
23	C_6H_5CH=C-CH_3 (*trans*)	**4l**	2 h		24	C_6H_5CH=C-CH_3 (*trans*)	**5l**	6 h	86

[a] Condition A : **2** (0.125 mmol), **3** (0.375 mmol), $BF_3{\cdot}OEt_2$ (30 mol%), toluene [0.0625 M], RT; Condition B : **2** (0.125 mmol), **3** (0.375 mmol), $Cu(OTf)_2$-$(C_6H_5O)_2P(O)OH$ (10 mol%), toluene [0.0625 M], RT. [b] Isolated yield.

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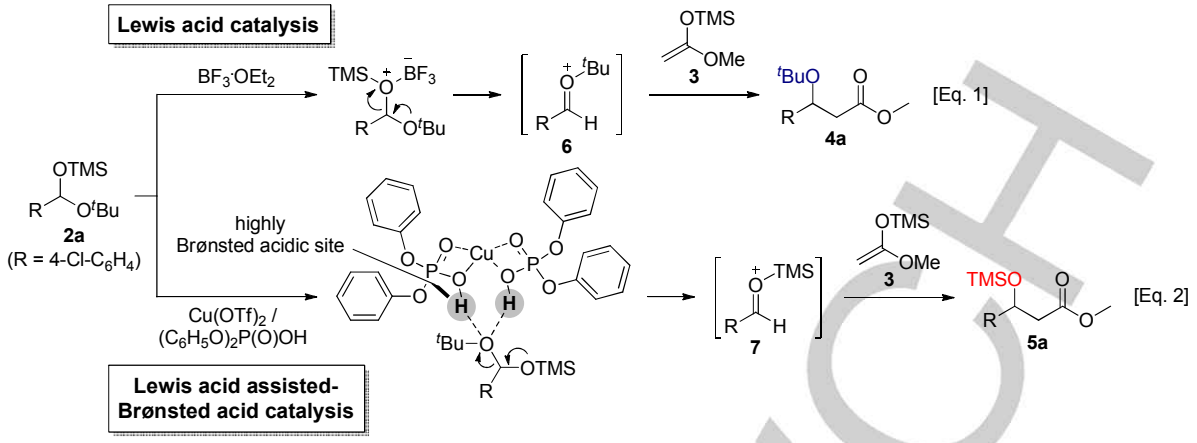


Scheme 5. Schematic illustration for chemoselective formation of oxocarbenium ions and Mukaiyama aldol reactions.

To support our hypothesis, we carried out the reaction under the following reaction conditions: mixed monosilyl acetal **2a**, silylenol ether **3**, $BF_3{\cdot}OEt_2$ in toluene at room temperature for 30 s. Fortunately, *tert*-butyl(4-chlorobenzylidene)oxocarbenium ion **6** was detected from the reaction mixture and analyzed by ESI-HRMS (positive ion mode) [Fig. 1].

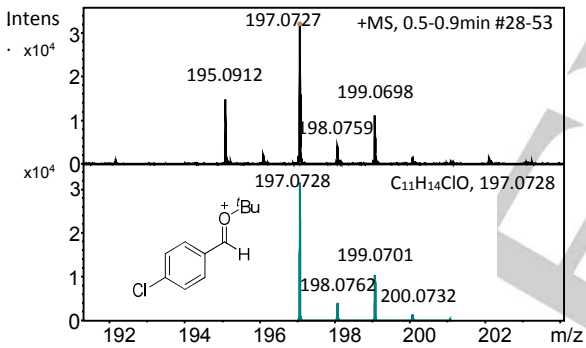
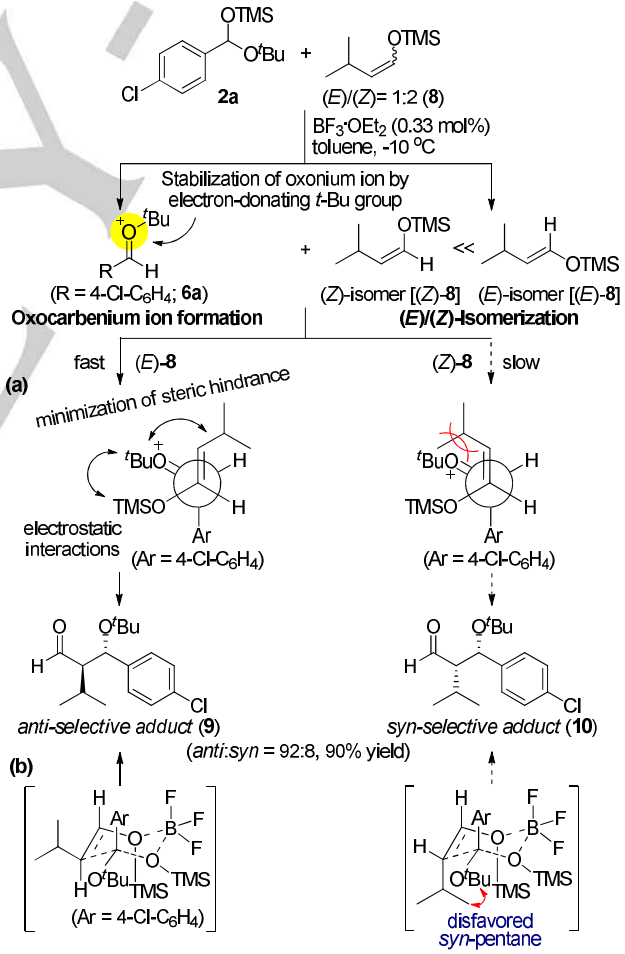


Figure 1. ESI-HRMS *m/z*: $[M]^+$ calcd for $C_{11}H_{14}ClO^+$ 197.0728; found 197.0727.

We then deduced the formation of the other oxocarbenium ion (**7**) via the dimeric Cu(II) complex with diphenyl phosphate ligands.[8] Cu(II)-phosphate complexes, the so-called "Lewis acid–assisted Brønsted acid (LBA)", arising from the Lewis acid activation of a Brønsted acidic site,[9] preferentially activate the Brønsted basic *O*-*tert*-butyl moiety to give transient oxocarbenium ion **7**.

Finally, we performed the Mukaiyama aldol reaction between mixed acetal **2a** and a 1:2 mixture of (*E*)- and (*Z*)-silyl enol ether **8**, derived from isovaleraldehyde, in toluene at –10 °C in the presence of $BF_3{\cdot}OEt_2$ (Scheme 6). To our surprise, *anti*-selective Mukaiyama aldol product **9** was obtained in excellent yield (90%) with extremely high level of diastereoselectivity (*anti*:*syn* = 92:8),[10] despite that the stereochemical outcome of Mukaiyama aldol reactions highly relies on the geometry of the silyl enol ether. The almost exclusive formation of *anti*-selective product **9** would be explained by the reaction of the stabilized *tert*-butyloxonium ion intermediate with the pre-equilibrated silyl enol ether from the (*E*)/(*Z*)-**8** isomerization.



Scheme 6. *anti*-Selective Mukaiyama aldol reaction with rational transition states: (a) Newman projection as open transition state model (b) Zimmerman–Traxler model as a six-membered closed transition state model.

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The oxonium ion, which forms selectively by the reaction of $BF_3 \cdot OEt_2$ from mixed monosilyl acetal **2a**, is stabilized by the electron-donating *tert*-butyl group and possess a long-enough life time to be detected by ESI-HRMS and to accommodate for the (*E*)/(*Z*) isomerization. Indeed, we observed and confirmed by NMR spectroscopy that the (*Z*)-configured silyl enol ether [(*Z*)-**8**] gradually isomerizes to (*E*)-configured isomer [(*E*)-**8**] under Lewis acidic conditions (see Supporting Information).[11] We observed almost perfect stereoselectivity from the reaction of our mixed monosilyl acetal with the isomeric mixture of silyl enol ethers.

The stereochemical outcome of the reaction can be rationalized based on the Newman projection as an open transition state model involving the oxocarbenium ion and silyl enol ether. The (*E*)-configured silyl enol ether gives raise to *anti*-product **9** with extremely high level of diastereoselectivity due to favoring electrostatic interactions, such as the ion-dipole interactions between the *tert*-butyl oxonium ion and the O-TMS group, and minimal steric hindrance between the *tert*-butyl oxonium ion and iso-propyl group, whereas the (*Z*)-configured silyl enol ether produces the *syn*-product **10** with low level of diastereoselectivity because of an unfavored steric hindrance between the *tert*-butyl oxonium ion and iso-propyl group.

The Zimmerman–Traxler six-membered closed transition state model may not be ruled out completely due to the involvement of the boron atom, which can be chelated to both silyloxy groups. In the transition state involving the use of the (*Z*)-configured silyl enol ether, the unfavorable *syn*-pentane interaction leads to the disfavored *syn*-adduct. The absolute configuration of *anti*-selective adduct **9** was determined by X-ray crystallography (see Supporting Information).

In summary, we have developed a novel protocol for the synthesis of mixed monosilyl acetal as a new and synthetically valuable functional group by the reaction of aldehydes with trimethylsilyl azide in the presence of sodium *tert*-butoxide as nucleophile. Salient features of our approach include (i) structurally different outcomes of *O*-protected β-hydroxyesters in the Mukaiyama aldol reaction can be obtained by the appropriate choice of oxophilic catalysts through Lewis acid catalysis or Lewis acid-assisted Brønsted acid catalysis and (ii) the extension of this protocol to *anti*-selective Mukaiyama aldol reactions with almost perfect stereoselectivity regardless of the ratio of (*E*)- and (*Z*)-silyl enol ethers.

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Keywords: Mixed acetal • Chemoselective • Mukaiyama aldol reaction • Stereoconvergent • Catalyst dependence

[1] a) T. Mukaiyama, M. Ohshima, N. Miyoshi, *Chem. Lett.* **1987**, *16*, 1121; b) L. F. Tietze, A. Dölle, K. Schiemann, *Angew. Chem. Int. Ed.* **1992**, *31*, 1372; *Angew. Chem.* **1992**, *104*, 1366; c) L. F. Tietze, K. Schiemann, C. Wegner, *J. Am. Chem. Soc.* **1995**, *117*, 5851; d) L. F. Tietze, C. Wulff, C. Wegner, A. Schuffenhauer, K. Schiemann, *J. Am. Chem. Soc.* **1998**, *120*, 4276; e) K. Maeda, H. Shinokubo, K. Oshima, *J. Org. Chem.* **1997**, *62*, 6429; f) K. Fujita, A. Inoue, H. Shinokubo, K. Oshima, *Org. Lett.* **1999**, *1*, 917; g) H. Shinokubo, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2255; h) H. Shinokubo, K. Oshima, K. Utimoto, *Chem. Lett.* **1995**, *24*, 461.

[2] H. Fujioka, T. Okitsu, T. Ohnaka, R. Li, O. Kubo, K. Okamoto, Y. Sawama, Y. Kita, *J. Org. Chem.* 2007, *72*, 7898.

[3] S.-i. Kiyooka, M. Shirouchi, Y. Kaneko, *Tetrahedron Lett*. **1993**, *34*, 1491.

[4] D. Sames, Y. Q. Liu, L. DeYoung, R. Polt, *J. Org. Chem.* **1995**, *60*, 2153.

[5] J. J. Song, F. Gallou, J. T. Reeves, Z. L. Tan, N. K. Yee, C. H. Senanayake, *J. Org. Chem.* **2006**, *71*, 1273.

[6] Alkali metal *tert*-butoxide as nucleophile, see: a) V. J. Gray, B. Slater, J. D. Wilden, *Chem. – Eur. J.* **2012**, *18*, 15582; b) S. A. DiBiase, G. W. Gokel, *J. Org. Chem.* **1978**, *43*, 447.

[7] Dipole moment values for TMS–CN and TMS–Cl, except for TMS–N_3, are reported in the literature. For TMS–CN, see: a) Å. Austerheim, T. Gramstad, *Acta Chem. Scand. B* **1985**, *39*, 583; b) M. J. Aroney, R. J. W. Le Fèvre, G. L. D. Ritchie, V. Ross, *J. Chem. Soc. B* **1966**, 188. However, average dipole moment values of these silanes are provided by the Pitt Quantum Repository (online chemistry databases): 4.38±1.08 D (for TMS–CN); 3.99±1.08 D (for TMS–N_3); 2.80±1.08 D (for TMS–Cl).

[8] T. Gilowiak, A. W. Szemik, *J. Crystallogr. Spectrosc. Res*. **1987**, *17*, 615.

[9] For reviews, see: a) H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; *Angew. Chem.* **2005**, *117*, 1958; b) H. Ishibashi, K. Ishihara, H. Yamamoto, *Chem. Rec.* **2002**, *2*, 177; For Lewis acid assisted Brønsted acid catalysis, see: c) S. Nakamura, M. Kaneeda, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8120; d) K. Ishihara, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 11179; e) K. Ishihara, S. Nakamura, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 12854; f) K. Ishihara, H. Nakamura, S. Nakamura, H. Yamamoto, *J. Org. Chem.* **1998**, *63*, 6444; g) K. Ishihara D. Nakashima, Y. Hiraiwa, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125* 24; h) S. Nakamura, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8131; i) K. Ishihara, S. Nakamura, H. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 4906; j) K. Ishihara, H. Ishibashi, H. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 3647; k) K. Ishihara, H. Ishibashi, H. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 1505.

[10] For representative examples of *anti*-selective Mukaiyama aldol reactions, see: a) S. E. Denmark, S. Fujimori, Modern Aldol Reactions; Vol. 2, Chapter 7 (Wiley–VCH, 2004); b) M. Wadamoto, N. Ozasa, A. Yanagisawa, H. Yamamoto, *J. Org. Chem.* **2003**, *68*, 5593; c) S. E. Denmark, G. L. Beutner, T. Wynn, M. D. Eastgate, *J. Am. Chem. Soc.* **2005**, *127*, 3774; d) J. Kobayashi, M. Nakamura, Y. Mori, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 9192; e) J. Saadi, M. Akakura, H. Yamamoto, *J. Am. Chem. Soc.* **2011**, *133*, 14248.

[11] For seminal report on isomerization of (E)/(Z)-silyl enolates under Lewis acidic conditions, see: Y. Yamashita, H. Ishitani, H. Shimizu, S. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 3292.

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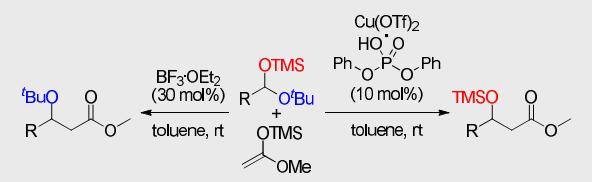

The unprecedented chemoselective Mukaiyama aldol reactions of mixed monosilyl acetals with silyl ketene acetals via discriminative activation of the alkoxy group on the acetal are achieved by different oxophilic catalysts.

S. M. Kim, H. S. Yang, H. Eum, H.-J. Ha, and J. W. Yang**

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Mixed Monosilyl Acetals and Catalyst-Dependent Chemoselective Mukaiyama Aldol Reactions

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