Mukaiyama Aldol Reaction of Ester Acceptors: Organoaluminums Catalyze Nucleophilic Addition of Ketene Silyl Acetals

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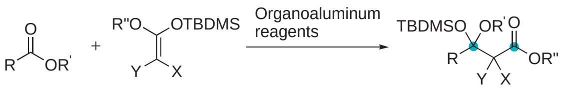
Organoaluminum reagents catalyze the addition of ketene silyl acetals to esters, affording the β-keto ester derivatives in good to excellent yields.

The Mukaiyama aldol reaction, i.e., the Lewis acid-mediated addition of enol silyl ethers to carbonyl compounds, is one of the most versatile carbon–carbon bond-forming reactions in current organic synthesis.[1,2] In contrast to everlasting advance of the stereoselective variants, the substrate scope of this reaction appears to have been settled. Recently, however, we accidentally met with an intriguing finding on the substrate scope in that methyl esters are good acceptor substrates in this reaction when organoaluminum compounds are employed as Lewis acid (Eq 1). Since the products are the protected form of β-keto esters corresponding to the cross-Claisen condensates,[3] we believe that this unexpected result has a large synthetic potential, which will be described in this communication.

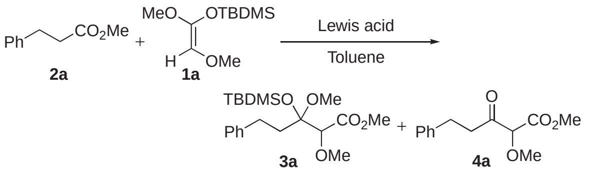


(1)

The key aspects of the finding are shown in Table 1 by the reactions of methyl ester **2a** and KSA **1a** promoted by various Lewis acids. Whereas $TiCl_4$ gave the moderate yield of β-keto ester **4a** (Entry 1),[4] $BF_3 \cdot OEt_2$ effected no reaction, only resulting in the recovery of **2a** (Entry 2). The situation was the same with other Lewis acids, such as $Sc(OTf)_3$ and TBSOTf, where no reaction occurred.

However, we were amazed to find that organoaluminum reagents promote the addition reaction of **1a** to **2a** rather than condensation: treatment of **2a** and KSA **1a** with $EtAlCl_2$ in toluene gave addition product **3a**[5] and keto ester **4a** in 63 and 14% yield, respectively (Entry 3).[6] When Me_3Al was employed, ester **3a** was obtained in 82% yield as the sole product (Entry 4). Moreover, the amount of Me_3Al could be reduced to 20 mol %, giving a higher yield of **3a**, albeit a slightly longer reaction time was required (Entry 5).

Table 1. Effect of Lewis acid

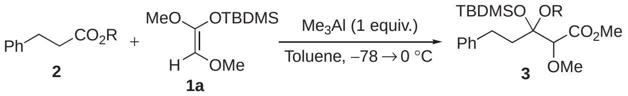


Entry	Lewis acid	Conditions	Yield of **3**/%	Yield of **4**/%
1	$TiCl_4$[a]	−78 °C, 4 h	—	47
2	$BF_3 \cdot OEt_2$[a]	−78 → 25 °C, 16 h	—	—
3	$EtAlCl_2$[a]	−78 °C, 4 h	63	14
4	Me_3Al[a]	−78 → 0 °C, 2 h	82	—
5	Me_3Al[b]	−78 → 0 °C, 6 h	86	—

[a]1.0 equiv. [b]0.2 equiv. [c]Syn/anti mixtures. Stereochemistry was not determined.

Effect of the alkoxy moiety in the ester acceptor was found to be significant (Table 2). Methyl ester was basically the sole viable substrate (Entry 1), and even the corresponding ethyl ester gave substantially lower yield of the adduct even after longer reaction time (Entry 2). Isopropyl and phenyl esters failed to react (Entries 3 and 4).

Table 2. Effect of the alkoxy moiety in the ester acceptor



Entry	R	Time/h	Yield/%
1[a]	Me	6	86
2	Et	18	25
3	*i*-Pr	18	—
4	Ph	18	—

[a]See Entry 5 in Table 1.

A typical procedure is as follows: ester **2a** (1 equiv.) and KSA **1a** (2.0 equiv.) was treated with Me_3Al (20 mol %) in toluene at −78 °C, and the reaction stirred for 6 h at 0 °C. The reaction was quenched with sat. aq. $NaHCO_3$. Extractive work-up followed by purification by silica-gel column chromatography gave the corresponding adduct **3a**[5] in 86% yield as a mixture of diastereomers.

In order to examine the scope of the reaction, we carried out the reactions of two KSAs, **1a** and **1b** (Figure 1), with various methyl esters as summarized in Table 3.

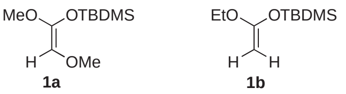
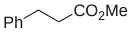
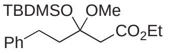
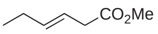
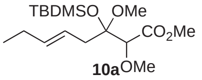
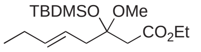
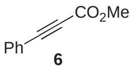
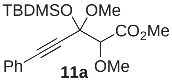
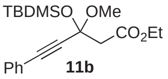
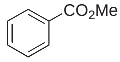
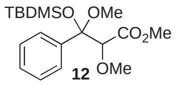
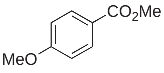
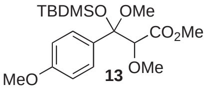


Figure 1.

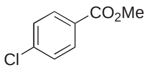
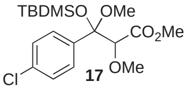
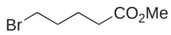
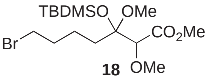
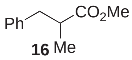
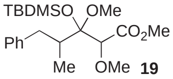
Addition of KSA **1b** to ester **2a** proceeded smoothly in the presence of 20 mol % of Me_3Al to give adduct **9**[5] in 72% yield (Entry 1). β,γ-Unsaturated ester **5** underwent the reaction with both of the KSAs, giving the corresponding adducts **10a**[5] and **10b**[5] in 82 and 63% yield, respectively (Entries 2 and 3). Similarly, the reactions of acetylenic ester **6** with KSAs **1a** and **1b** proceeded smoothly to afford adducts **11a**[5] and **11b**[5] in high yields (Entries 4 and 5). The reaction of aromatic ester **7** with KSA **1a** afforded **12**[5] in quantitative yield (Entry 6). Moreover, ester **8** having an electron-donating *p*-methoxy group

Table 3. Me_3Al-mediated Mukaiyama aldol reaction

Entry[a]	Ester	KSA	Time/h	Product	Yield/%
1	 **2a**	**1b**	7	 **9**	72
2	 **5**	**1a**	12	 **10a**	82[b]
3		**1b**	2	 **10b**	63
4	 **6**	**1a**	1	 **11a**	77[b]
5		**1b**	2	 **11b**	63
6	 **7**	**1a**	18	 **12**	quant.[b]
7	 **8**	**1a**	19	 **13**	86[b]

[a] All reactions were performed with Me_3Al in toluene at −78 °C and the temperature raised to 0 °C. [b] Syn/anti mixtures.

Table 4. MAO-mediated Mukaiyama aldol reaction

Entry[a]	Ester	KSA	Time/h	Product	Yield/%
1	 **14**	**1a**	2	 **17**	95[b] (0)[c]
2	 **15**	**1a**	2	 **18**	78[b] (0)[c]
3	 **16**	**1a**	4	 **19**	74[b] (7)[c]

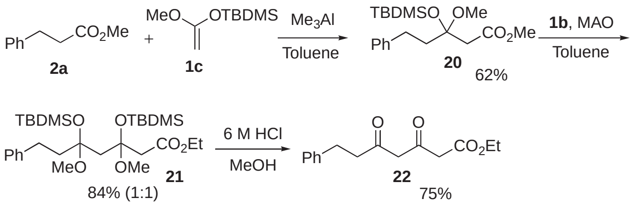
[a] All reactions were performed with MAO in toluene at −78 °C and the temperature raised to 0 °C. [b] Syn/anti mixtures. [c] Yield by the Me_3Al-protocol. Almost full recovery of the starting material.

on the aromatic ring was also a good substrate for the reaction (Entry 7).

Application of the reaction to *p*-chlorobenzoate **14** needs to be addressed (Entry 1, Table 4). While the reaction of **14** with KSA **1a** under the conditions described above gave no adduct, screening of other aluminum reagents revealed that MAO nicely promotes the reaction (MAO[7] 1.1 equiv. of toluene, −78 to 0 °C), giving adduct **17**[5] in 95% yield.[8]

Along the same lines, Me_3Al was ineffective for the reactions of the bromo-bearing ester **15** and the α-methyl substrate **16**. However, MAO nicely promoted the reaction of esters **15** and **16** to give the respective adduct in 78 and 74% yield (Entries 2 and 3).

Scheme 1 shows the application to dual reactions. The first addition of KSA **1c** to ester **2a** was promoted by Me_3Al to give ester **20**, which, in turn, was treated with KSA **1b** in the presence of MAO to produce ester **21**[5] in good yield.[9] The dual adduct **21** was hydrolyzed by treatment with 6 M HCl in MeOH (r.t., 1 h) to give the corresponding diketo ester **22**[10] in 75% yield, representing the potential utility of the reaction in the context of poly-carbonyl compounds.



Scheme 1.

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This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

References and Notes

1 a) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503. b) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, 1011. c) K. Saigo, M. Osaki, T. Mukaiyama, *Chem. Lett.* **1975**, 989. d) T. Mukaiyama, M. Hayashi, *Chem. Lett.* **1974**, 15.

2 For reviews, see: a) T. Mukaiyama, in *Org. React.*, ed. by W. G. Dauben, Wiley, New York, **1982**, Vol. 28, p. 203. b) R. Mahrwald, *Chem. Rev.* **1999**, *99*, 1095. c) T. K. Hollis, B. Bosnich, *J. Am. Chem. Soc.* **1995**, *117*, 4570.

3 For reviews on *Claisen condensation*, see: a) C. R. Hauser, B. E. Husdon, Jr., in *Org. React.*, ed. by R. Adams, W. E. Bachmann, L. F. Fieser, J. R. Johnson, H. R. Snyder, Wiley, New York, **1942**, Vol. 1, p. 266. b) B. R. Davis, P. J. Garratt, in *Comprehensive Organic Synthesis*, ed. by B. M. Trost, I. Fleming, Pergamon, Oxford, **1991**, Vol. 2, p. 795.

4 For selected examples of the crossed Claisen condensation, see: a) T. Misaki, R. Nagase, K. Matsumoto, Y. Tanabe, *J. Am. Chem. Soc.* **2005**, *127*, 2854. b) A. Iida, K. Takai, T. Okabayashi, T. Misaki, Y. Tanabe, *Chem. Commun.* **2005**, 3171. c) A. Iida, S. Nakazawa, T. Okabayashi, A. Horii, T. Misaki, Y. Tanabe, *Org. Lett.* **2006**, *8*, 5215, and references cited therein.

5 All new compounds were fully characterized by spectroscopic means and combustion analysis. See Supporting Information, which is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

6 To our knowledge, 1,2-addition of KSA to simple esters has not been studied. For isolated examples using acetylene carboxylates or lactones as acceptors, see: a) M. Onaka, T. Mimura, R. Ohno, Y. Izumi, *Tetrahedron Lett.* **1989**, *30*, 6341. b) K. Homma, H. Takenoshita, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1898. c) R. Csuk, M. Schaade, *Tetrahedron Lett.* **1993**, *34*, 7907.

7 Modified MAO, hydrolysate of Me_3Al–*i*-Bu_3Al (2:1), Al = 6 wt % in toluene, was kindly donated from Tosoh Finechem Co., Ltd.

8 For use of MAO as highly active Lewis acid catalyst, see: M. Akakura, H. Yamamoto, *Synlett* **1997**, 277; For other examples of MAO-accelerated processes, see: S. Yamanoi, T. Matsumoto, K. Suzuki, *Tetrahedron Lett.* **1998**, *39*, 9727.

9 When the reaction was performed with Me_3Al, the yield was only 24%.

10 Ester **22** existed in an enol form.

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