Pergamon

Tetrahedron Letters 43 (2002) 1469–1472

TETRAHEDRON
LETTERS

A highly chemoselective Mukaiyama aldol reaction of saturated aldehyde over unsaturated aldehyde with enol tris(2,6-diphenylbenzyl)silyl ether

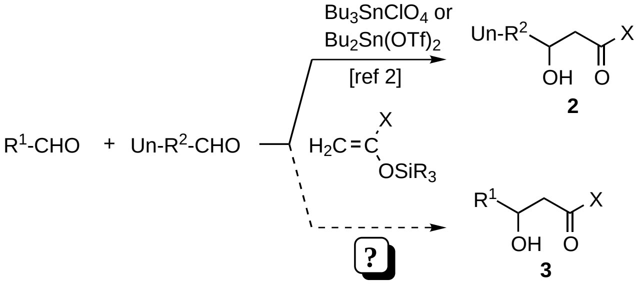
Seiji Shirakawa and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502, Japan

Received 2 November 2001; revised 17 December 2001; accepted 21 December 2001

Abstract—An exceedingly high chemoselective Mukaiyama aldol reaction of saturated aldehydes in the presence of unsaturated aldehydes (benzaldehyde and α,β-enals) has been realized for the first time by using the structurally unique enol tris(2,6-diphenylbenzyl)silyl ether under the influence of $BF_3 \cdot OEt_2$ as a Lewis acid. Among unsaturated aldehydes, benzaldehyde is found to be more reactive than α,β-enals. The structural uniqueness of the enol tris(2,6-diphenylbenzyl)silyl ether can be visualized by X-ray crystallography as well as ^1H and ^{13}C NMR spectroscopy. © 2002 Elsevier Science Ltd. All rights reserved.

Due to powerful yet highly selective carbon–carbon bond formations, the Mukaiyama aldol reaction has found numerous applications in selective organic synthesis,[1] and a number of related modifications have been elaborated for this purpose. Among these, the chemoselective functionalization between two different carbonyl acceptors is a synthetically useful operation and is closely related to the chemistry of molecular recognition. Recently, the chemoselective aldol reaction of α,β-enals with ketene silyl acetals has been achieved under the influence of organotin Lewis acids in competition with saturated aldehydes.[2] Surprisingly, however, despite several other reports on the preferential attack of certain nucleophiles to α,β-unsaturated carbonyl substrates over the corresponding saturated carbonyls,[3,4] the reverse selectivity, i.e. the chemoselective aldol reaction of saturated aldehydes (R^1-CHO) in the presence of unsaturated aldehydes (Un-R^2-CHO), has never been developed to a useful level due to the lack of appropriate reagents (Scheme 1). Indeed, attempted Lewis acid-promoted aldol reaction between saturated and unsaturated aldehydes with a series of enol silyl ethers resulted in a total lack of chemoselectivity, as shown in Scheme 2. During the course of our recent investigations on the chemistry of the functionalized, bowl-shaped tris(2,6-diphenylbenzyl)metal moiety,[5–8] we studied the chemoselective Mukaiyama aldol reaction with the structurally unique enol tris(2,6-diphenylbenzyl)silyl ether **1a** (hereafter, enol TDS ether; TDS = tris(2,6-diphenylbenzyl)silyl). Here we wish to report the hitherto unknown, unusual discriminative ability of enol TDS ether **1a** in the Mukaiyama aldol reaction between saturated and unsaturated aldehydes under the influence of $BF_3 \cdot OEt_2$ as a Lewis acid, giving an aldol product **3** almost exclusively over aldol **2** (Schemes 1 and 2).



Scheme 1.

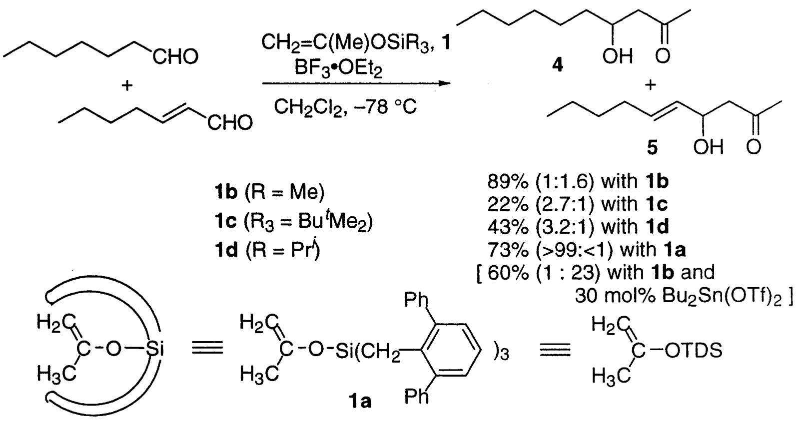
The ordinary Lewis acid-promoted aldol reaction between heptanal and *trans*-2-heptenal (1.1 equiv. each) with enol trimethylsilyl ether of acetone (CH_2=C(Me)$OSiMe_3$) in the presence of $BF_3 \cdot OEt_2$ (2.2 equiv.) gave rise to a mixture of two different aldols **4** and **5** in a ratio of 1:1.6. Switching the silyl moiety of CH_2=C(Me)$OSiR_3$ from trimethylsilyl to *t*-butyldimethylsilyl (*t*-$BuMe_2Si$) and triisopropylsilyl (*i*-

---

Keywords: chemoselectivity; Mukaiyama aldol reaction; aldehyde; silicon.

* Corresponding author. Tel./fax: +00 81 75 753 4041; e-mail: maruoka@kuchem.kyoto-u.ac.jp

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00036-9



Scheme 2.

Pr_3Si) resulted in a slight increase in chemoselectivity [**4**/**5**=2.7:1 and 3.2:1, respectively]. In marked contrast, however, the corresponding enol TDS ether **1a** showed virtually complete discriminative ability (**4**/**5**=>99:<1), leaving unsaturated aldehyde intact. Such a discrimination pattern is totally opposite to those in chemoselectivity reported previously [**4**/**5**=1:23 with catalytic $Bu_2Sn(OTf)_2$ and **1b**].[2,3] Other examples including various combinations of saturated and unsaturated aldehydes are listed in Table 1. Several characteristic features of the present chemoselective aldol reaction follow. (1) In general, unsaturated aldehydes such as benzaldehyde and α,β-enals are highly reluctant toward the Lewis acid-promoted aldol reaction with enol TDS ether **1a** in the presence of saturated aldehyde under ordinary aldol conditions. Such unreactivity can be observed even in combination with sterically more hindered aldehyde (entry 7 versus 6 and 17 versus 16). (2) In contrast, enol TDS ether **1a** showed none of the chemoselectivity in the combination of the two saturated aldehydes (entries 8 and 9 versus 6 and 7). (3) Among unsaturated aldehydes, benzaldehyde is found to be more reactive than α,β-enal (entry 21). (4) Discrimination between saturated and even homoconjugated α-phenylated aldehyde appears feasible (entries 22 and 23). (5) The amount of $BF_3{\cdot}OEt_2$ as a Lewis

Table 1. Chemoselective aldol reaction between two different aldehydes with enol silyl ethers[a]

Entry	Enol silyl ether	Two different aldehydes	% Yield[b] (ratio)[c]
1	**1b**	Hexyl-CHO+Bu-CH=CHCHO	89 (1:1.6)
2	**1c**		22 (2.7:1)
3	**1d**		43 (3.2:1)
4	**1a**		73 (>99:<1)[d]
5	**1a**		81 (71:1)[d,e]
6	**1b**	*c*-Hexyl-CHO+Bu-CH=CHCHO	96 (1.2:1)
7	**1a**		79 (>99:<1)[d]
8	**1b**	*c*-Hexyl-CHO+Hexyl-CHO	79 (1:1.2)
9	**1a**		57 (1:1.5)
10	**1b**	Hexyl-CHO+PhCHO	80 (1:1.4)
11	**1a**		75 (45:1)[d]
12	**1b**	$Ph(CH_2)_2CHO$+PhCHO	69 (1:1.8)
13	**1a**		63 (40:1)[d]
14	**1b**	*c*-Hexyl-CHO+PhCHO	83 (1:2.5)
15	**1a**		85 (23:1)
16	**1b**	Ph_2CHCHO+PhCH=CHCHO	61 (1:1)
17	**1a**		63 (>99:<1)[d]
18	**1b**	$Ph(CH_2)_2CHO$+PhCH=CHCHO	82 (4.1:1)
19	**1a**		84 (>99:<1)[d]
20	**1b**	PhCHO+PhCH=CHCHO	90 (5.4:1)
21	**1a**		75 (34:1)[d]
22	**1b**	$Ph(CH_2)_2CHO$+PhCH(Me)CHO	82 (2.4:1)
23	**1a**		64 (21:1)

[a] Unless otherwise specified, the aldol reaction was carried out with enol silyl ether **1** (1 equiv.) and two different aldehydes (1.1 equiv. each) (R^1-CHO and Un-R^2-CHO) in the presence of $BF_3{\cdot}OEt_2$ (2.2 equiv.) in CH_2Cl_2 at −78°C for 0.5–1.5 h.

[b] Isolated yield of **3** (X=Me) and **2** (X=Me).

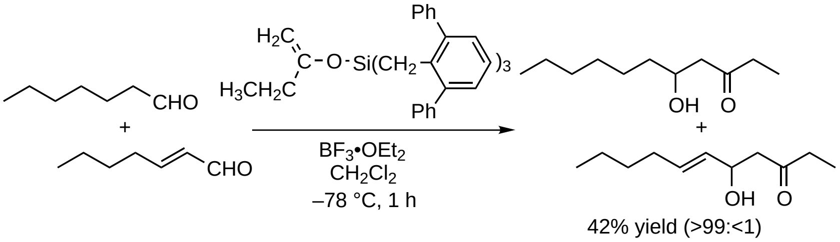
[c] The ratio of two aldol products **3** (X=Me) and **2** (X=Me) was determined by ^1H NMR analysis.

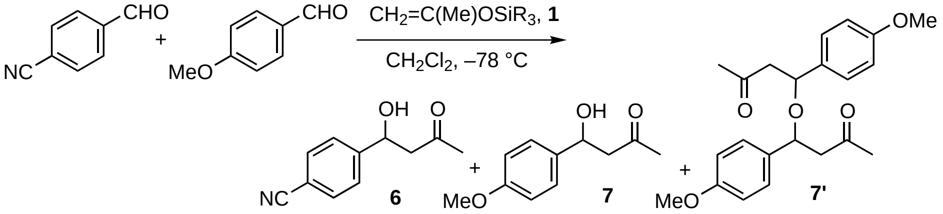
[d] Determined by capillary GLC analysis after conversion to diols by treatment of two aldol products with MeLi (3 equiv.) in THF.

[e] Use of catalytic $BF_3{\cdot}OEt_2$ (30 mol%).

acid can be reduced to catalytic (~30 mol%) without affecting the chemoselectivity (entry 5). (6) A similar tendency was also observed with other Lewis acids such as $TiCl_4$, $SnCl_4$, and Me_2AlCl.[9]

A similar high chemoselectivity was also observable in the aldol reaction between heptanal and *trans*-2-heptenal (1.1 equiv. each) with enol TDS ether of 2-butanone in the presence of $BF_3{\cdot}OEt_2$ (2.2 equiv.).





enol silyl ether	Lewis acid (equiv)	yield	ratio of **6**:(**7**+**7'**) [**7**:**7'**]
1b	BF_3•OEt_2 (2.2)	63%	1 : 1 (1.7:1)
1a	BF_3•OEt_2 (2.2)	45%	>99 : <1
1b	$Bu_2Sn(OTf)_2$ (0.3)	84%	<1 : >99 (1:1.5)

Another interesting feature includes the chemoselective aldol reaction of *p*-substituted benzaldehydes on the electronic effect of *p*-substituents of these benzaldehydes. While catalytic $Bu_2Sn(OTf)_2$ (30 mol%) gives *p*-anisaldehyde-derived aldol **7** and its dimerization product **7′** preferentially, our silylating agent **1a** reacted reluctantly to furnish *p*-cyanobenzaldehyde-derived aldol **6** exclusively.

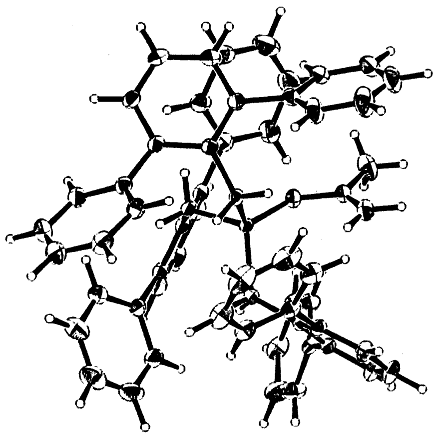
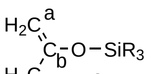


Figure 1. ORTEP diagram of the enol tris(2,6-diphenylbenzyl)silyl ether **1a**.

The structural uniqueness of the enol TDS ether **1a** can be visualized by X-ray crystallography as well as NMR spectroscopy. As shown in Fig. 1, the X-ray structure of **1a** indicated a well-oriented π,π interaction between one nearby phenyl and the isopropenyl group;[10] this is also supported by the upfield shift of isopropenyloxy moiety by ^1H and ^{13}C NMR spectral study of the enol TDS ether **1a** in $CDCl_3$, where the upfield shift of isopropenyl protons in **1a** compared to other silyl analogues such as trimethylsilyl, *t*-butyldimethylsilyl, and triisopropylsilyl derivatives was clearly observed.

Although the origin of the observed chemoselectivity using the enol TDS ether **1a** is unclear at present, the electronic stabilization of the isopropenyloxy moiety with one nearby phenyl group of tris(2,6-diphenylbenzyl)silyl group via the π,π interaction (Fig. 1) seems to be essential to achieve the high discriminative ability in the Mukaiyama aldol reaction. Further clarification of such unusual chemoselectivity using **1a** is currently underway, and will be reported in due course.



1

^1H & ^{13}C NMR Data	H(a)	H(c)	C(a)	C(b)	C(c)
1a	δ 2.34, 2.58	δ 0.92	δ 90.17	δ 152.38	δ 22.66
1b (R = Me)	δ 4.05, 4.06	δ 1.78	δ 91.16	δ 155.83	δ 22.84
1c (R_3 = Bu^tMe_2)	δ 4.03	δ 1.76	δ 91.20	δ 156.12	δ 22.78
1d (R = Pr^i)	δ 4.01, 4.05	δ 1.81	δ 90.45	δ 156.26	δ 22.82

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (No. 13853003) from the Ministry of

Education, Culture, Sports, Science and Technology, Japan.

References

1. Reviews of aldol reactions: (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203; (b) Carreira, E. M. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, 1999; Vol. 3, p. 997.
2. Chen, J.; Otera, J. *Synlett* **1997**, 29.
3. (a) Hanyuda, K.; Hirai, K.; Nakai, T. *Synlett* **1997**, 31; (b) Marko, I. E.; Leung, C. W. *J. Am. Chem. Soc.* **1994**, *116*, 371; (c) Mori, A.; Ohno, H.; Inoue, S. *Chem. Lett.* **1992**, 631; (d) Mikami, K.; Terada, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 5456; (e) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; Chapter 3.
4. Chemoselective aldol reaction of less hindered saturated aldehydes: (a) Maruoka, K.; Saito, S.; Yamamoto, H. *Synlett* **1994**, 439; (b) Marx, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 178.
5. Chemistry of bowl-shaped tris(2,6-diphenylbenzyl)metal moiety: (a) Iwasaki, A.; Kondo, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 10238; (b) Sasaki, K.; Kondo, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 411.
6. Reaction bowls: (a) Goto, K.; Tokitoh, N.; Okazaki, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1124; (b) Sasaki, T.; Goto, K.; Tokitoh, N.; Okazaki, R. *J. Org. Chem.* **1996**, *61*, 2924; (c) Sasaki, T.; Goto, K.; Okazaki, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2223; (d) Goto, K.; Holler, M.; Okazaki, R. *J. Am. Chem. Soc.* **1997**, *119*, 1460.
7. Molecule capsules: (a) Meissner, R. S.; Rebek, J., Jr.; Mendoza, J. *Science* **1995**, *270*, 1485; (b) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50; (c) Kang, J.; Hilmersson, G.; Santamaria, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3650; (d) Kang, J.; Santamaria, J.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 7389.
8. Concave reagents: (a) Luning, U.; Muller, M.; Gelbert, M.; Peters, K.; von Schnering, H. G.; Keller, M. *Chem. Ber.* **1994**, *127*, 2297; (b) Hagen, M.; Luning, U. *Chem. Ber./Recueil* **1997**, *130*, 231; (c) Ross, H.; Luning, U. *Tetrahedron Lett.* **1997**, *38*, 4539; (d) Lofflwe, F.; Hagen, M.; Luning, U. *Synlett* **1999**, 1826.
9. Attempted aldol reaction of a 1:1 mixture of heptanal and benzaldehyde with **1a** or **1b** in the presence of $TiCl_4$, $SnCl_4$ or Me_2AlCl gave the following results: 52% (1.1:1) with **1b**/$TiCl_4$; 41% (19:1) with **1a**/$TiCl_4$; 48% (1:1.1) with **1b**/$SnCl_4$; 64% (>99:<1) with **1a**/$SnCl_4$; 47% (4.5:1) with **1b**/Me_2AlCl; 47% (>99:<1) with **1a**/Me_2AlCl. $(i\text{-}PrO)_2TiCl_2$ was found to be unreactive for effecting the chemoselective aldol reaction with **1a**.
10. The single-crystal of enol TDS ether **1a** was obtained by recrystallization from benzene/hexane solvents. Crystal structure data for **1a**: $C_{60}H_{50}OSi{\cdot}C_6H_6$, $M_w = 893.25$, triclinic, space group P-1, $a = 13.0354$, $b = 13.9145$, $c = 31.9467$ Å, $V = 5101.9$ Å^3, $Z = 4$, $D_{calcd} = 1.163$ g cm^{-1}, $R_1 = 0.055$.