A NOVEL DIASTEREOSELECTIVITY IN THE ALDOL REACTION OF CYCLIC KETENE SILYL ACETALS WITH COBALT-COMPLEXED AND UNCOMPLEXED PROPYNALS

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The aldol reaction of seven-membered ketene silyl acetal (**9**) with cobalt-complexed propynals afforded the erythro isomer in a highly stereoselective manner, while the high threo selectivity could be realized with uncomplexed simple propynals.

KEYWORDS enolsilane; cobalt-complexed propynal; aldol reaction; diastereoselectivity; erythro isomer; threo isomer

The aldol reaction of enolsilanes with aldehydes in the presence of Lewis acid (Mukaiyama reaction)[1] has become one of the most popular tools for constructing of a framework with 1,3-dioxygen functionality.[2-4] But so far, very little information[5,6] on the stereochemistry of the Mukaiyama reaction is available in spite of its broad utility in organic synthesis.[1-4]

Recently we introduced the cobalt-complexed propynal[7] into the aldol condensation with silyl enol ethers, where the erythro isomer was predominantly obtained irrespective of the stereochemistry of the starting silyl enol ethers. We report here a novel diastereoselectivity in the aldol reaction of cyclic ketene silyl acetals (**7–9**) with cobalt-complexed propynals (**1–3**) and uncomplexed simple propynals (**4–6**).

The aldol reaction of cyclic ketene silyl acetals (**7–9**) with cobalt-complexed propynals (**1–3**) was carried out in methylene chloride at -78°C in the presence of titanium tetrachloride[8] to give the aldol products[9] after decomplexation with cerium ammonium trinitrate (CAN)[10] in methanol at 0°C. Several representative results obtained under the standard condition[11] are summarized in Table I. On the other hand, the aldol reaction with uncomplexed propynals (**4–6**) under the same condition without treatment with CAN also provided the condensation products[9] as shown in Table II.

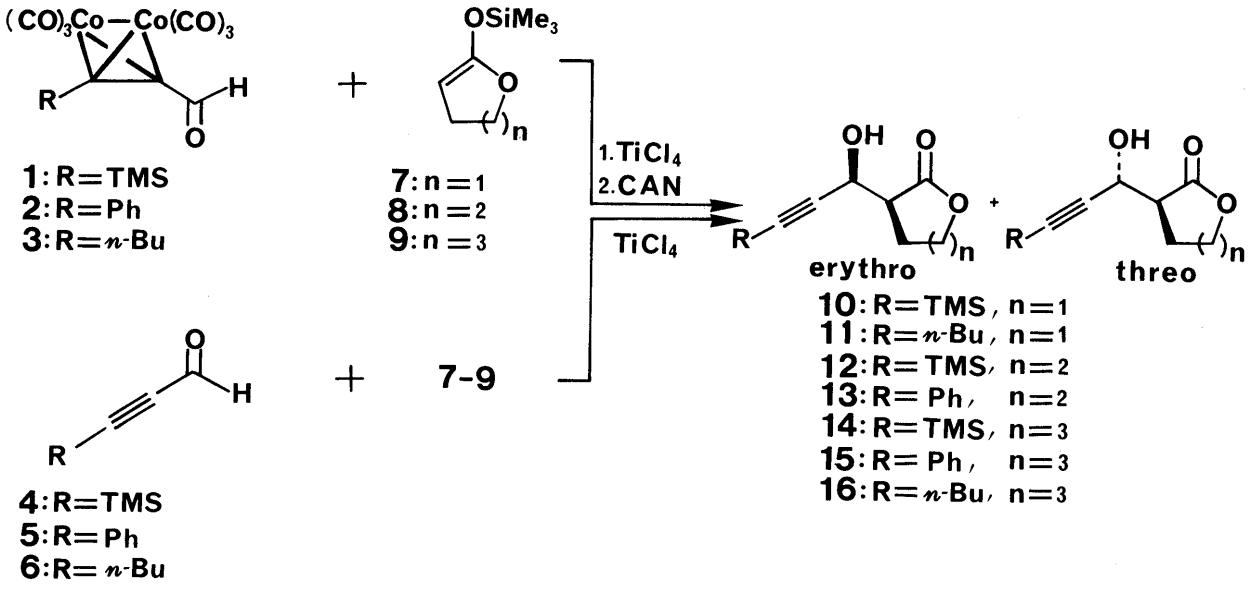

Table I. Aldol Reaction of Cyclic Ketene Silyl Acetals with Cobalt-Complexed Propynals

Entry	Aldehyde	Ketene silyl acetal	Aldol product	Yield(%)[a] E:T[b]
1	**1**	**7**	**10**	74(80:20)[c]
2	**3**	**7**	**11**	77(87:13)[c]
3	**1**	**8**	**12**	55(80:20)
4	**2**	**8**	**13**	87(80:20)
5	**1**	**9**	**14**	77(92:8)
6	**2**	**9**	**15**	88(95:5)
7	**3**	**9**	**16**	87(92:8)

a) Yields of products isolated, after decomplexation, by flash chromatography. b) E=erythro, T=threo. Determined by 400 MHz ^{1}H-NMR spectra unless otherwise stated. c) Ratio of each pure isomer isolated by flash chromatography.

Table II. Aldol Reaction of Cyclic Ketene Silyl Acetals with Uncomplexed Simple Propynals

Entry	Aldehyde	Ketene silyl acetal	Aldol product	Yield(%)[a] E:T[b]
1	**4**	**7**	**10**	84(50:50)[c]
2	**6**	**7**	**11**	56(48:52)[c]
3	**4**	**8**	**12**	90(20:80)
4	**5**	**8**	**13**	83(36:64)
5	**4**	**9**	**14**	91(5:95)
6	**5**	**9**	**15**	88(22:78)
7	**6**	**9**	**16**	87(6:94)

a) Yields of products isolated after flash chromatography. b) E=erythro, T=threo. Determined by 400 MHz ^{1}H-NMR spectra unless otherwise stated. c) Ratio of each isomer isolated by flash chromatography.

The erythro isomer was stereoselectively obtained in the reaction of cyclic ketene silyl acetals (**7**-**9**) with cobalt-complexed propynals regardless of the size of the ring in cyclic acetals. Especially in the case of seven-membered acetal (**9**), a high erythro selectivity could be attained (entry 5-7) as shown in Table I. Table II indicates several significant features. i) Five-membered acetal (**7**) did not show any characteristic stereoselectivity at all (entries 1,2). ii) Six-membered acetal (**8**) gave the threo isomer in a moderate selectivity[12] (entries 3,4). iii) The threo isomer was obtained in a highly stereoselective manner in the case of seven-membered acetal (**9**)[13](entries 5 and 7). Thus, the threo selectivity was greatly enhanced with the increase of the size of the ring in cyclic acetals. It is noteworthy that the remarkable contrast in the diastereoselectivity between the cobalt-complexed and uncomplexed propynal occurred in the case of seven-membered acetal (**9**), where the former showed a high erythro selectivity whereas the latter afforded the threo isomer in a highly stereoselective manner.

The mechanism for the erythro selectivity in the reaction of the cobalt-complexed propynal with the cyclic ketene silyl acetal could be tentatively rationalized in terms of the modified synclinal transition state[14] via acyclic cationic species. On the other hand, the threo selectivity in the reaction between seven- (and six-) membered acetal and the uncomplexed simple propynal might be explained by the six-membered chair-like transition state proposed previously by Chan.[6a] However, it is still hard to explain the fact that the threo/erythro ratio was surprisingly improved by changing the size of the ring in cyclic ketene silyl acetals from five to seven.

In summary, our newly developed procedure can provide stereoselectively not only the erythro, but also the threo isomer from the same cyclic ketene silyl acetal simply by changing the aldehyde counterpart from the cobalt-complexed to the uncomplexed propynal. The synthesis potentiality of this procedure is further enhanced by the fact that the triple bond has been well proved to be the versatile precursor for various functionalities.

Further studies on the mechanistic aspect as well as an application for the synthesis of a natural product is currently under active investigation.

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8) BF_3 OEt_2, $SnCl_4$, $EtAlCl_2$, and TMSOTf also showed the good erythro selectivity, but less effective than $TiCl_4$.
9) All new compounds gave satisfactory spectral and analytical data. Stereochemical assignment was made by careful analysis of the chemical shift value and the coupling constant[2,3] of the propargyl proton in each isomer in the 400 MHz ^{1}H-NMR spectra.
10) A.M. Montana, K.M. Nicholas, and M.A. Khan, J. Org. Chem., **53**, 5193(1988), and references cited therein.
11) A typical experimental procedure is as follows: a solution of 1 M $TiCl_4$ in CH_2Cl_2 (0.35 ml, 0.35 mmol) was added dropwise to a stirred solution of **3** (124 mg, 0.31 mmol) and **9** (88 mg, 0.47 mmol) in dry CH_2Cl_2 (5 ml) at -78°C. After stirring for 1 h, a sat. NH_4Cl solution was added to the reaction mixture and the CH_2Cl_2 layer was separated, washed with water, dried, and concentrated. The residue was dissolved in MeOH (5 ml) and CAN (719 mg, 1.3 mmol) was slowly added to the solution at 0°C. The brownish color of the reaction mixture gradually faded away. MeOH was evaporated off and the residue was taken up in AcOEt. The AcOEt solution was washed with water and brine, dried, and concentrated to dryness. Flash chromatography of the residue with n-hexane/AcOEt (1/1) gave **16** (61 mg, 87%) as a mixture of erythro/threo (92/8).
12) The aldol reaction of trimethylsilyloxycyclohexene with **4**, for example, gave the corresponding condensation products nonselectively (erthro/threo=44/56): C. Mukai, K. Nagami, and M. Hanaoka, unpublished result.
13) In sharp contrast to this result, the seven-membered silyl enol ether (trimethylsilyloxycycloheptene), on treatment with **4**, did not show any characteristic selectivity (erythro/threo=43/57): C. Mukai, K. Nagami, and M. Hanaoka, unpublished result.
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(Received December 4, 1989)