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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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Intermolecular/Intramolecular Sequential Aldol Reaction

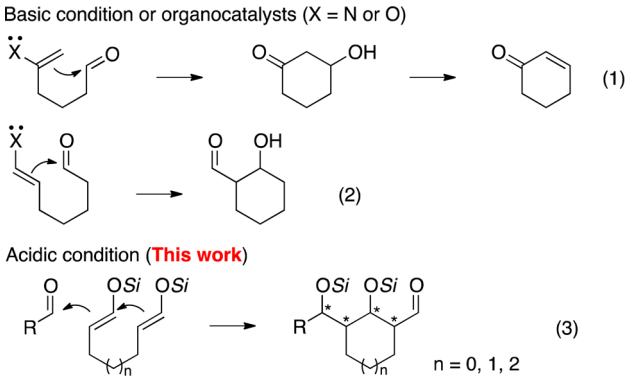
Atsuto Izumiseki* and Hisashi Yamamoto*

Molecular Catalyst Research Center, Chubu University, 1200 Matsumoto-cho, Kasugai 487-8501, Japan

Supporting Information

ABSTRACT: The first example of intermolecular/intramolecular sequential aldol reaction of disilyl enol ethers is described. This strategy enables the formation of five-, six-, and seven-membered ring products. Four or more contiguous stereogenic centers are created with high levels of relative stereochemical control.

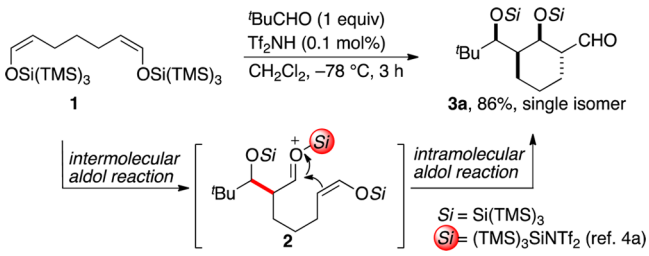
The aldol reaction is one of the most powerful synthetic tools for carbon−carbon bond formation.[1] Although numerous variants of classical intermolecular aldol reactions have been developed, the intramolecular aldol reaction is rather limited except under basic conditions leading directly to cyclic enones (eq 1).[2] Recently, the catalytic *enol exo* type



intramolecular aldol reactions of 1,7-dicarbonyl compounds were reported by List for the synthesis of cyclic β-hydroxy aldehydes (eq 2).[3] In contrast, to the best of our knowledge, intramolecular aldol reaction under acidic conditions has not been reported so far. Here we report the first example of sequential intermolecular aldol followed by intramolecular aldol reaction of disilyl enol ethers using a Brønsted acid or Lewis acid catalyst based on our super silyl technology (eq 3).[4]

The required disilyl enol ether **1** could be prepared directly from the $CHO(CH_2)_5CHO$ (pimelaldehyde) stereoselectivity (66% yield; >99% *ZZ* isomer). The sequential aldol reaction proceeded with amazing diastereoselectivities: the first aldol reaction of disilyl enol ether **1** with aldehyde and 0.1 mol % triflimide (Tf_2NH) in CH_2Cl_2 at −78 °C resulted in the intermediary aldehyde **2**,[4a] and the successive intramolecular aldol reaction proceeded smoothly to give the six-membered ring aldol product **3a** as a single diastereomer (86% yield; *dr* > 99%, out of eight possible diastereomers) (Scheme 1). A notable characteristic of this method is that the four new contiguous stereogenic centers were generated in this reaction

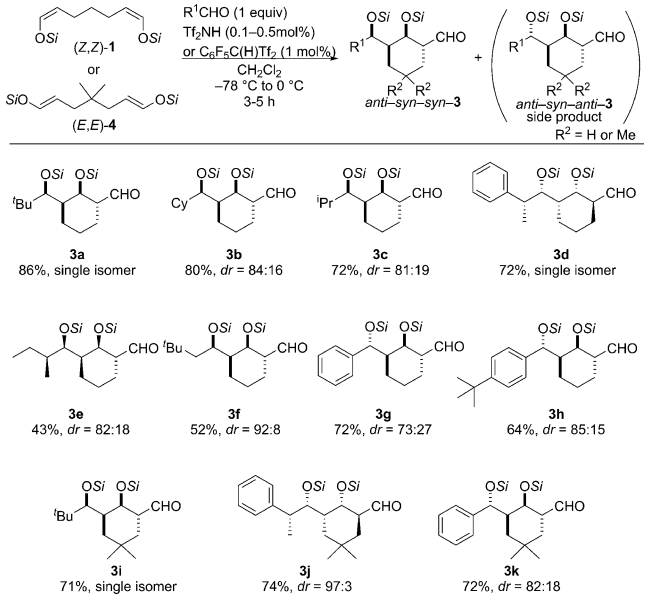
Scheme 1. Intermolecular/Intramolecular Sequential Aldol Reaction



with virtually complete diastereo control by a single manipulation. The relative configurations *anti-syn-syn* for aldehyde **3a** were determined from subsequent addition of phenyl Grignard reagent followed by single-crystal X-ray analysis.[5]

Gratified by this result, we examined the intermolecular/intramolecular sequential aldol reaction with various aldehydes (Table 1). Reaction of α-branched aliphatic aldehydes showed equally good yields and high diastereoselectivities of the six-

Table 1. Scope of the Aldehyde Substrate in the Intermolecular/Intramolecular Sequential Aldol Reaction[a]



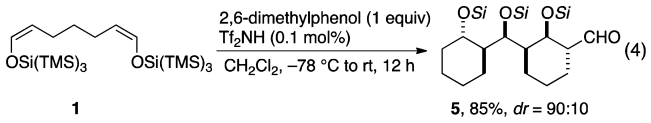
[a] *dr* = *anti-syn-syn*-**3**/*anti-syn-anti*-**3**, *Si* = $Si(TMS)_3$.

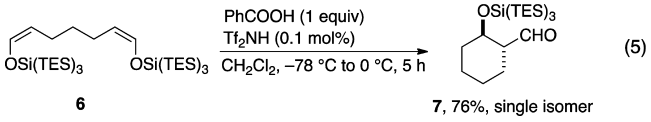
Received: December 20, 2013
Published: January 15, 2014

   dx.doi.org/10.1021/ja413008a | *J. Am. Chem. Soc.* 2014, 136, 1308−1311

membered ring aldol products **3a**, **3b**, and **3c**.[6] The use of chiral aldehydes showed high Felkin control in conjunction with *syn* selectivity providing five adjacent stereocenters (products **3d** and **3e**).[4h] Linear aliphatic gave **3f** with high diastereoselectivities and moderate yields. Aromatic aldehydes afforded **3g** and **3h** in good yields and moderate diastereoselectivities.[7] The (*E*,*E*)-disilyl enol ether **4** was prepared as a single diastereomer (70% yield; >99% *EE* isomer) by iridium catalyzed isomerization following the protocol from Miyaura and co-workers.[8] The aldol reaction proceeded smoothly to give the six-membered ring products **3i**–**3k** in good yields and excellent diastereoselectivities, with the same diastereomer as the reaction from (*Z*,*Z*)-disilyl enol ether **1**.[9]

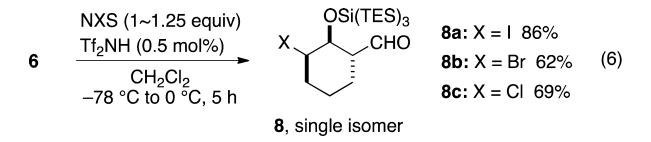
Subsequently, the protonation/intramolecular sequential aldol reaction was tested. Reaction of disilyl enol ether **1** with 2,6-dimethylphenol and 0.1 mol % Tf_2NH as a catalyst gave none of the six-membered β-siloxyaldehye, and β,δ,ζ-trisiloxyaldehyde **5** was produced by protonation/intramolecular aldol/intermolecular aldol/intramolecular aldol cascade reaction, probably due to the slow protonation compared to the subsequent rapid aldol reaction (eq 4).[10] Obviously, the initial





rapid protonation and slower intermolecular aldol reaction should be able to stop the following intermolecular aldol reaction. Indeed, combined use of protonation of TES-type super silyl [tris(triethylsilyl)silyl] enol ether **6** with more acidic benzoic acid and Tf_2NH succeeded in stopping at the first aldol cyclization stage to give the cyclic aldol product in an almost completely stereoselective manner (eq 5).

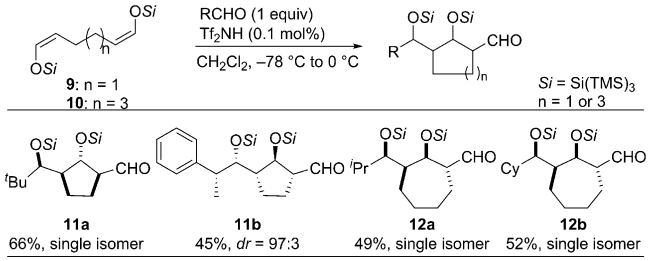
Next, the halogenation followed by intramolecular aldol cyclization was examined.[11] Reaction of TES-type super silyl enol ether **6** with NXS (X = I, Br, Cl) and 0.5 mol % Tf_2NH as a catalyst gave the six-membered γ-halo-β-siloxyaldehyde (eq 6), with which three contiguous stereogenic centers were



generated. NIS, NBS, and NCS reacted smoothly with TES-type super silyl enol ether **6**, affording products **8a**, **8b**, and **8c** in good yields as single diastereomers.

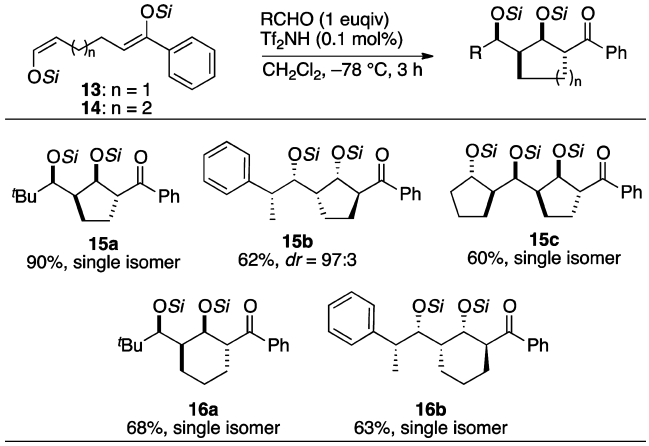
The present methodology can be extended to five- and seven-membered ring syntheses (Table 2). Reaction of disilyl enol ether **9** with aldehydes 0.1 mol % Tf_2NH as a catalyst gave the five-membered ring aldol products **11a** and **11b** in moderate yields and excellent diastereoselectivities. The use of disilyl enol ether **10** gave seven-membered ring aldol products **12a** and **12b** in moderate yields as a single isomer. Interestingly, the five-membered ring aldol product **11a** was found to have *anti-anti-syn* stereochemistry, with a different stereochemistry as the reaction from disilyl enol ether **1**.[12]

Table 2. Formation of Five- and Seven-Membered Ring Aldol Adducts



The present method has been applied to a nonsymmetrical disilyl enol ether derivative of ketoaldehyde: as expected, reaction of 6- and 7-ketoaldehyde-derived disilyl enol ethers (**13** and **14**) with aldehydes resulted in excellent diastereomeric five- and six-membered ring aldol adducts (Table 3). Interestingly, the silyl enol ether of aldehyde reacted first and then the subsequent cyclization took place.

Table 3. Intermolecular/Intramolecular Sequential Aldol Reaction with Ketoaldehyde-Derived Disilyl Enol Ethers[a]



[a] *Si* = $Si(TMS)_3$.

A proposed transition state for the intermolecular/intramolecular sequential aldol reaction of the six-membered ring process is shown in Figure 1. (*Z*,*Z*)-Disilyl enol ether **1** with aldehyde produces *anti-syn-syn* product of the intermolecular/intramolecular sequential aldol reaction: It is generally accepted that the reaction proceeds through an open antiperiplanar transition state.[4h,13] The Lewis acid (Si^1) coordinates to the aldehyde oxygen atom in a position *cis* to the aldehyde hydrogen atom to minimize steric repulsion.[14] There must be steric interactions (1) between the super-silyloxy group (OSi^2) and Lewis acid (Si^1) and (2) between OSi^2 and OSi^3. The antiperiplanar transition state structure **17** (the first intermolecular aldol reaction)[15] and **18** (the second intramolecular aldol reaction) are free from those interactions and produced the *anti-syn-syn* aldol product. The (*E*,*E*)-disilyl enol ether **4** with aldehyde was found to be *anti-syn-syn* stereochemistry; the same diastereomer forms (*Z*,*Z*)-disilyl enol ether **1** with aldehyde. For (*E*,*E*)-disilyl enol ether **4**, the transition state structure **19** is expected. The first intermolecular aldol reaction produced *syn* stereochemistry. For the second intramolecular aldol reaction, transition states structure **20** is disfavored because of the steric repulsions between the Lewis acid (Si^2)

dx.doi.org/10.1021/ja413008a | J. Am. Chem. Soc. 2014, 136, 1308–1311

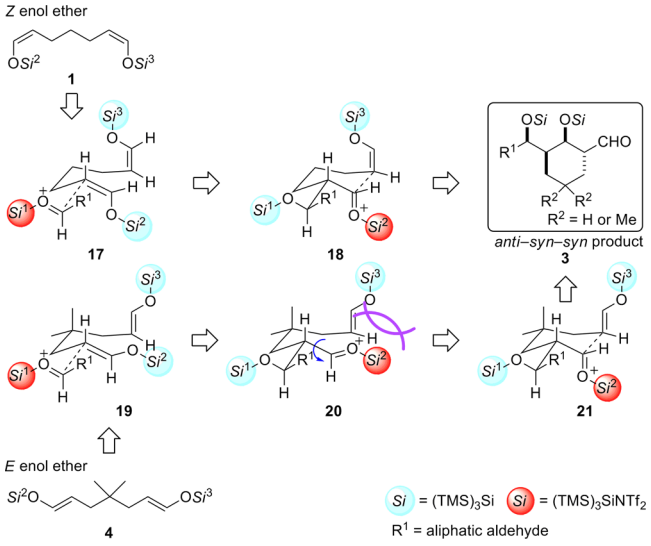


Figure 1. Proposed transition states of the six-membered ring aldol product.

and OSi^3 groups. Thus, C−C bond rotation occurred before the second aldol reaction. The transition state **21** is the most favorable, thus rationalizing the formation of the *anti-syn-syn* aldol product.[16]

In contrast, (*Z*,*Z*)-disilyl enol ether **9** with aldehyde was found to be *anti-anti-syn* stereochemistry of the five-membered ring in intermolecular/intramolecular sequential aldol reaction (Figure 2). For (*Z*,*Z*)-disilyl enol ether **9**, the transition state

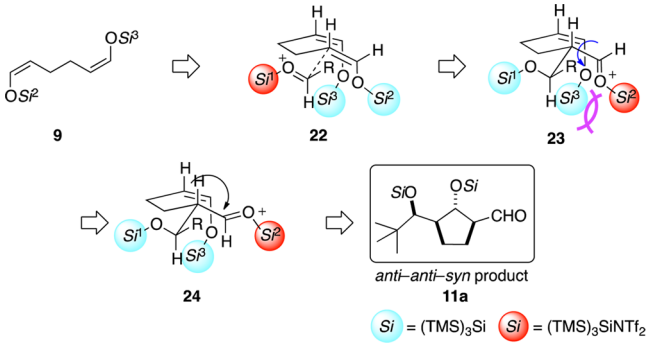


Figure 2. Proposed transition states of the five-membered ring aldol product.

structure **22** is favored. The first intermolecular aldol reaction showed *syn* selectivity. In the second intramolecular aldol reaction, transition states structure **23** is disfavored because of the steric repulsions between the Lewis acid (Si^2) and OSi^3 groups. In this case, C−C bond rotation occurred prior to the following cyclization. The result showed the transition state **24** is the most favorable, thus rationalizing the formation of the *anti-anti-syn* aldol product.

In summary, we have developed a new strategy for a highly diastereoselective intermolecular/intramolecular sequential aldol reaction of disilyl enol ethers and aldehyde, and formation of new five-, six-, and seven-membered ring aldol products. An attractive feature of this new strategy is the ability to create four or more contiguous stereogenic centers in a single process with high levels of stereochemical control by super silyl groups. Moreover, this method applied intermolecular protonation and halogenation followed by intramolecular aldol reaction with two or three stereogenic centers in diastereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

izumiseki@isc.chubu.ac.jp

hyamamoto@isc.chubu.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction. This work was supported by a Grant-in-Aid for Scientific Research (No. 23225002), Advanced Catalytic TransFormation Program for Carbon Utilization, the Uehara Memorial Foundation, Nippon Pharmaceutical Chemicals Co., Ltd, and Advance Electric Co., Inc.

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(5) For derivatization and single crystal X-ray analysis see Supporting Information.

(6) The minor isomer seems to be the *anti-syn-anti* product by single crystal X-ray analysis and NMR analysis.

(7) The first aldol reaction of aromatic aldehyde proceeds *anti* selectivities. Please see Supporting Information for details.

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(16) Calculation of this mechanism is ongoing with the collaboration of Dr. Akakura.