Table III. Comparison of $^{13}C$ NMR Chemical Shifts due to Steric Interactions for 7-Methylglaucine Derivatives 4 and 6 and 8-Methyl-*trans*-decahydroisoquinoline Derivatives 16 and 17

| carbon | 4 | 6 | carbon | 16 | 17 |
|---|---|---|---|---|---|
| 4 | 29.6 | 22.5 | 3 | 25.8 | 19.4 |
| 5 | 53.3 | 50.7 | 2 | 58.2 | 55.0 |
| 6a | 65.8 | 62.9 | 9 | 71.9 | 70.7 |
| *N*-methyl | 43.8 | 34.7 | *N*-methyl | 42.2 | 33.2 |
| 7-methyl | 13.5 | 14.6 | 8-methyl | 12.1 | 18.9 |
| 8 | 110.5 | 108.2 | | | |

second study was especially helpful in the analysis of 4 and 6. The preferred conformations of 4 and 6 were assigned on the basis of steric interactions as depicted with Dreiding models and are illustrated in 14 and 15 (Chart II). These two diastereomers were examined in comparison with the 8-methyl-*trans*-decahydroquinoline isomers 16 and 17,[29] and the sterically induced shifts were interpreted as follows (see Table III). In the *trans*-7-methylglaucine isomer (15), 1,3-diaxial interactions between the *N*-methyl group and C4-hydrogen cause a shielding at the C4 carbon (-7.1 ppm) and the *N*-methyl carbon (-9.1 ppm). Shielding was also observed in this stereoisomer at C5 (-2.6 ppm) and C6a (-2.9 ppm). Comparable shifts were observed in 8$\alpha$-methyl-*trans*-decahydroquinoline (17) for the *N*-methyl (-9.0 ppm), C2 (-3.2 ppm), C3 (-6.4 ppm), and C9 (-1.2 ppm) positions. The C7-methyl moiety was shielded (-1.1 ppm) in the cis isomer (14) due to its axial orientation as also occurs in the 8$\beta$-methyl-*trans*-decahydroquinoline (16). Conversely, the equatorial orientation of the C7-methyl group in the trans-isomer 15 caused an upfield shift (-2.3 ppm) of the C8-carbon due to C7-methyl/C8-H interactions.

The racemic mixtures represented by *cis*-7-methylglaucine (4/5) and *trans*-7-methylglaucine (6/7) were utilized as substrates with *Fusarium solani* and *Aspergillus flavipes*. In cell suspensions of *F. solani*, only *cis*-7-methylglaucine was metabolized, and to the expected extent of 50%, presumably due to stereoselective oxidation of the 6a*S*,7*S* stereoisomer, 4 (assuming the organism retains its 6a*S* stereochemical preference as observed with (*S*)-(+)-glaucine[2]). Cell-suspension cultures were used since only sluggish metabolism was observed in growing cultures. *A. flavipes* also metabolized only *cis*-7-methylglaucine, again to the expected extent of 50%, presumably due to stereoselective oxidation of the 6a*R*,7*R* stereoisomer, 5 (assuming the organism retains its 6a*R* stereochemical preference as observed with (*R*)-(-)-glaucine[3]). Thus, in both organisms, an overall cis elimination appears to be operative. We recognize, as was suggested earlier for methyl-blocked steroid substrates,[4,5] that the presence of an alkyl substituent in the 7-position may hinder approach of the substrate to the requisite enzyme(s) (reactions were observed to be slower than with glaucine) and that stereochemical preference may be altered. Thus, such studies will require confirmation with the appropriate isotopically labeled substrates.[5]

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**Registry No.** (*S*)-(+)-1, 475-81-0; 2, 22212-26-6; (*R*)-(-)-3, 38325-02-9; (±)-cis-4/5, 84681-50-5; (±)-*trans*-6/7, 84681-51-6; 8, 72498-26-1; 16, 52008-64-7; 17, 55970-12-2; formaldehyde, 50-00-0.

# Fluoride Ion Catalyzed Aldol Reaction between Enol Silyl Ethers and Carbonyl Compounds

Eiichi Nakamura,† Makoto Shimizu,† Isao Kuwajima,*† J. Sakata,‡ K. Yokoyama,‡ and R. Noyori*‡

*Department of Chemistry, Tokyo Institute of Technology, Ookayama, Meguro, Tokyo 152, Japan, and Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan*

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A new aldol reaction effected by the reaction of enol trimethylsilyl ethers and a quaternary ammonium fluoride is reported. Under the influence of a catalytic amount of tetrabutylammonium fluoride at low temperatures, enol silyl ethers react with various aldehydes to give the corresponding aldol trimethylsilyl ethers in fair to good yields. The silyl group of these products can be smoothly removed under mild conditions. Ketones, epoxides, and esters do not serve as electrophiles in this reaction. The reaction proceeds in a regiospecific manner with respect to the enol silyl ethers; the reactions of two regioisomers of 2-methylcyclohexanone with benzaldehyde cleanly give the respective regioisomeric aldol products. The reaction of 4-*tert*-butyl-1-methyl-2-(trimethylsiloxy)cyclohexene proceeds exclusively by the axial attack of the electrophile, making a strong contrast with the related cases reported on this cyclohexanone system. The aldol addition of a ketone and an aldehyde can be performed without the isolation of the enol silyl ether of the ketone by effecting both the silylation of the ketone and the aldol reaction with the aid of a fluoride anion. The characteristic behavior of the enolate species in this reaction can be rationalized by considering a mobile equilibrium in which the combination of fluorotrimethylsilane and a quaternary ammonium enolate functions as the key controlling factor.

The aldol reaction is one of the standard tools for creating new carbon–carbon bonds,[1] but its utility in organic synthesis has been severely limited because of the difficulties in controlling the course of the reaction. Attempts to effect the heterocoupling of carbonyl compounds have been fraught with troubles. Since the aldol reaction is controlled by a series of equilibria centered around the aldol anion 2 shown in Scheme I, which do not necessarily favor the adduct formation, undesired self- or polycon-

† Tokyo Institute of Technology.
‡ Nagoya University.

(1) Reviews: (a) Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1. (b) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1972; pp 629–689.

0022-3263/83/1948-0932$01.50/0 

Scheme I. Aldol Reaction

densation products often form, unless some deliberate measures are taken. Regioselectivity of the reaction was also problematic. Moreover, the strong, uncontrolled reaction conditions normally employed[1] gave dehydration products, which may suffer further side reactions.

Three basically different methodologies have been devised recently to circumvent these synthetic problems. The first one is the directed aldol reaction procedure developed initially by Wittig[2] that uses the lithio derivatives **3** in place of the enolate intermediate **1**. The second method involves Lewis acid catalyzed electrophilic attack of carbonyl compounds (or their acetals) onto enol ether derivatives. Whereas the initial phase of such an approach was centered in the use of enol ethers and acetals,[3] recent developments have immensely broadened the synthetic utility. Thus, the reactions of enol silyl ethers[4] under various catalysts, for example, titanium tetrachloride[5] and trimethylsilyl triflate,[6] have proven useful for the regio and (sometimes) stereoselective[6] synthesis of aldol-type compounds. Finally, enolate anions with Lewis acidic metal cations undergo controlable aldol reactions. Halomagnesium[7] and bromozinc enolates[8] are some of the earlier examples. Preformed lithium enolates[9] add to aldehydes at very low temperature with retention of the regiochemistry of the starting enolates. Aluminum[10] and boron enolates[11] are relatively new in this field, yet have already attained considerable success. Especially, the latter is deemed promising for the control of the stereochemistry of this reaction, which is attracting much interest in relation to the challenge of acyclic stereocontrol.[12] Reactions

Table I. Fluoride-Catalyzed Aldol Reaction of 1-(Trimethylsiloxy)cyclohexene (5) and Benzaldehyde[a]

| fluoride salt (equiv to 5) | solvent | reaction condns: temp, °C | reaction condns: time, h | % yield of aldol |
|---|---|---|---|---|
| $(n\text{-}C_4H_9)_4NF$ (0.06) | THF | −78 | 3.5 | 84 |
| $(n\text{-}C_4H_9)_4NF$ (1.0) | THF | −78 | 2.0 | 63 |
| $PhCH_2Me_3NF$ (0.3) | THF | −40 | 2.0 | 66 |
| $(C_2H_5)_4NF$ (0.04) | THF | −25 | 16 | 64 |
| CsF (0.04) | THF/$CH_3CN$ | 60 | 45 | 20 |
| CsF (1.0) | THF/$CH_3CN$ | 60 | 4.5 | 9 |
| KF (0.05) | THF | 60 | 61 | 0 |
| KF (0.06) | $CH_3CN$ | 60 | 61 | 23 |
| KF (1.0) | THF | 60 | 24 | 0 |
| KF (1.0) | $CH_3CN$ | 60 | 18 | 41 |
| KF (0.17)/crown ether[b] | $C_6H_6$ | 23 | 16 | 50 |
| NaF (0.07) | $CH_3CN$ | 60 | 61 | 10 |
| NaF (1.0) | $CH_3CN$ | 60 | 4.5 | 24 |
| LiF (0.13) | $CH_3CN$ | 60 | 41 | 0 |
| LiF (1.5) | $CH_3CN$ | 60 | 40 | 0 |

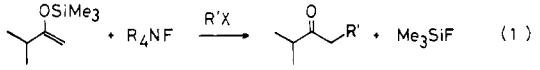
[a] For details, see the Experimental Section. [b] Dicyclohexyl-18-crown-6 (0.1 equiv with respect to KF) was added. No aldol product was obtained in THF solvent.

of tin[13] and zirconium[14] enolates are also receiving attention in relation to the stereochemical problems. A very recent report described the reaction of α-mercurio ketones.[14c]

We recently reported a new aldol reaction,[15] an elaboration of yet another concept, relying on rapid chemical trapping of the aldol anion **2** by silylation to control the reaction. This aldol reaction showed a number of intriguing characteristics, the full details of which are described herein.

## Results and Discussion

The extremely high affinity of the fluoride anion toward the silicon atom parallels the high homolytic bond energy of the Si–F linkage.[16] The utilization of this property for protonolysis of Si–O[17] has been known for sometime, and the potential of the fluoride-mediated generation of nucleophiles[18] was initially demonstrated by the regiospecific alkylation of enol silyl ethers (eq 1).[19]



(1)

It is a rather fortuitous situation that we have to employ a large soft cation, e.g., the tetraalkylammonium cation, to make effective use of the nucleophilic property of the fluoride anion, since fluorine atoms bind strongly with most usual metal cations. Thus, a fluoride-mediated re-

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(4) (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462, 4464. (b) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (c) Review: Rasmussen, J. K. *Synthesis* **1977**, 91.
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(10) (a) Jeffery, E. A.; Meisters, A. *J. Organomet. Chem.* **1974**, *82*, 307. (b) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705.
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(18) Nucleophilic reactions of (perhalophenyl)trimethylsilane in the presence of KF (in DMF) were recognized in the early seventies but not exploited further. (a) Webb, A. F.; Sethi, D. S.; Gilman, H. *J. Organomet Chem.* **1970**, *21*, 61. (b) Ishikawa, H.; Isobe, K.-I. *Chem. Lett.* **1972**, 435.
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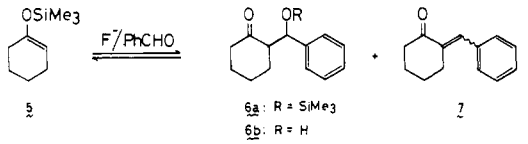
action such as eq 1 necessarily generates an enolate species with a soft countercation, the chemistry of which has been less explored than that of more commonly encountered metal enolates.

In this context, the fluoride-catalyzed aldol reaction aroused much of our interest. Because of the cation, the




reaction proved to be readily reversible at various stages, yet clean and controllable. The success of the reaction was shown to depend on the unique system of silicon–fluorine combinations.

**Reaction Conditions.** The reaction of enol silyl ethers **5** and **8** and benzaldehyde was examined with respect to a variety of metal and tetraalkylammonium salts and solvents. KOMe/18-crown-6 complex, which initiated similar reactions with ethyl (trimethylsilyl)acetate,[20] effected very slow consumption of the starting materials at lower temperatures (<−25 °C) in THF and at higher temperatures (∼0 °C) produced a very complex mixture mainly consisting of enones such as **7**.

On the other hand, fluoride salts worked best in this reaction. The effect of the countercation in the reaction of **5** and benzaldehyde is found in Table I: tetraalkylammonium fluorides serve as the most effective catalyst, affording the aldol adduct **6b** in high yield. The reaction with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) proceeded smoothly even at −78 °C. Benzyltrimethylammonium fluoride (BTAF), while best in the alkylation reaction (eq 1),[19] was less satisfactory here, giving a small amount of enone **7** (∼10%) even at low temperature (−78–0 °C). The use of tetraethylammonium fluoride was not advantageous either. Metal fluorides, sparingly soluble in organic solvents, necessitated the use of a large amount of salts and a higher temperature in order to obtain a reasonable reaction rate. Choice of the solvent appears to be crucial in the metal fluoride catalysis. The reactive fluoride anion from potassium fluoride and dicyclohexyl-18-crown-6 was capable of effecting the aldol reaction in benzene, but the expected aldol was not obtained in THF. Cesium fluoride was far less satisfactory than BTAF, whereas it has found some recent successful applications in related cases.[21]

The aldol product was isolated as the silyl ether **6a** by diluting the reaction mixture with dry hexane followed by the usual aqueous extractive workup. Isolation of the aldol **6b** was achieved by treating the crude reaction mixture with aqueous acetic acid or, more smoothly, with aqueous HCl, which does not change the stereochemistry of **6a** on conversion to **6b**. Potassium fluoride in methanol effected desilylation with appreciable scrambling of the threo–erythro stereochemistry. Although slow addition of water to the reaction mixture afforded the aldol **6b** directly, this was sometimes irreproducible. Notably, neither the enone **7** nor other polycondensation products formed under TBAF catalysis. Aprotic solvents such as THF, acetonitrile, dimethoxyethane, dimethylformamide, or dimethyl sulfoxide gave good results in TBAF-catalyzed reactions (Table II). Diethyl ether may also be employed. Consideration of the physical properties renders THF as the solvent of choice for general use.

Table II. TBAF-Catalyzed Reaction of 1-(Trimethylsiloxy)cycloheptene (8) and Benzaldehyde in Various Solvents[a]

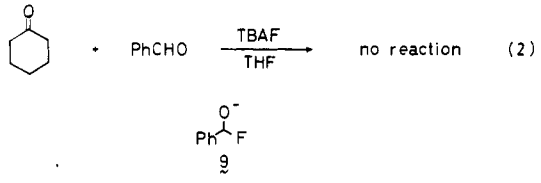
| solvent | temp, °C | time, h | % yield of aldol |
|---|---|---|---|
| tetrahydrofuran | −78 | 2.5 | 77 |
| acetonitrile | −35 | 2.5 | 62 |
| dimethoxyethane | −78 | 2.5 | 62 |
| ether | −35 | 16.5 | 72 |
| *N,N*-dimethylformamide | −78 | 2.5 | 70 |
| dimethyl sulfoxide | 23 | 0.2 | 79 |

[a] For details, see the Experimental Section.

There was found an optimum range in the amount of the catalyst. A stoichiometric amount of TBAF caused a considerable decrease of the product yield (Table I), and too small an amount of the catalyst sometimes caused the formation of 1:2 adducts (vide infra). Thus, good results were obtained with 5–20 mol % of TBAF. It is notable that, in contrast to the aldol reactions of lithium enolates,[9a] the present reaction tolerates a wide range of reaction conditions. The reactions were performed with equal success at −30 to −78 °C for 2–4 h (See Table III).

The fluoride anion is moderately basic.[22] In fact, the formation of anionic species from highly acidic substrates is fairly fast. The Michael addition of malondinitrile onto methyl acrylate (1:2 adduct) proceeded rapidly at room temperature, while the reaction of diethyl malonate was sluggish (3 mol % of TBAF in THF) and did not proceed any further than the initial 1:1 adduct formation.[23]

The basicity of the fluoride anion, however, is low enough to leave normal ketones and aldehydes intact. Treatment of an equimolar mixture of cyclohexanone and benzaldehyde with 10 mol % of TBAF for 41 h at room temperature in THF resulted in the total recovery of both reactants (eq 2).




These observations indicate the following points related to the present aldol reaction: (1) The fluoride anion may not work as a base under the reaction conditions, and the occasional formation of enone products, e.g., **7**, in some unoptimized runs is not due to the fluoride anion itself but due to basic species generated by the interaction of fluoride anion and organosilicon compounds. (2) The participation of a species like the fluoride–aldehyde adduct **9** is unlikely, for it would have caused condensation of the carbonyl compounds in eq 2.

**Scope and Limitations.** A variety of enol silyl ethers and carbonyl compounds undergo the fluoride-catalyzed reaction to give aldols or the corresponding silyl ethers (Table III). The reactions were quite clean under the optimum conditions described above. The silyl ethers employable for the reaction include those of alkyl aryl

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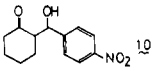
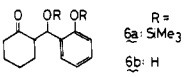
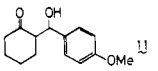
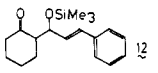
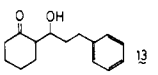
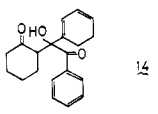
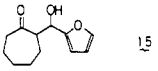
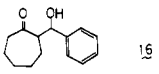
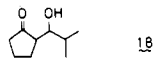
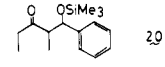
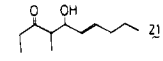
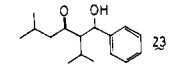
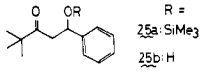
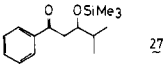
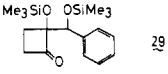
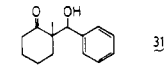
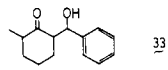
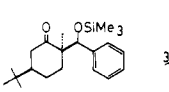
Table III. Aldol Reaction between Enol Silyl Ethers and Carbonyl Compounds[a]

| entry | enol silyl ether | aldol | condns: temp, °C | condns: time, h | % yield[b] | threo/erythro ratio |
|---|---|---|---|---|---|---|
| 1 |  5 |  10 | −40 | 1 | 92[c] | 2:5 |
| 2 | |  R = 6a: SiMe3, 6b: H | −78 | 3.5 | 80 | |
| 3 | | | −78 | 3.5 | 84 | 3:2 |
| 4 | |  11 | −78 | 5 | 58[d] | 3:2 |
| 5 | |  12 | −78 | 2 | 59 | *m* |
| 6 | |  13 | −20 | 2 | 37 | *m* |
| 7 | |  14 | −25 | 20 | 31[e] | *m* |
| 8 |  8 |  15 | −25 | 22 | 95 | 1:2 |
| 9 | |  16 | −78 | 6.5 | 80 | 1:2 |
| 10 |  17 |  18 | −30 | 14 | 52[f] | *j* |
| 11 |  19 |  20 | −78 | 5 | 70 | *m* |
| 12 | |  21 | −78 | 24 | 48[g] | *m* |
| 13 |  22 |  23 | −25 | 22 | 59 | 3:5[k] |
| 14 |  24 |  R = 25a: SiMe3, 25b: H | −25 | 16 | 57[h] (7)[i] | *n* |
| 15 | | | −78 | 2.5 | 42 | *n* |
| 16 |  26 |  27 | 5 | 14 | 39 (7)[i] | *n* |
| 17 |  28 |  29 | −78<br>−30 | 3<br>0.5 | 69 (11)[i] | (3:7 or 7:3)[l] |
| 18 |  30 |  31 | −30 | 2 | 62 | 3:7 |
| 19 |  32 |  33 | −20 | 2 | 68 | 1:1 |
| 20 |  34 |  35a | −35 | 1.5 | 68 | 6:4 |

[a] See the Experimental Section for the details. [b] Isolated yield. [c] Aldehyde (4%) was recovered. [d] Aldehyde (43%) was recovered. [e] Ketone (50%) was recovered. [f] $Me_3SiF$ (2 equiv) was added. [g] Enol silyl ether was used in excess (30%). [h] $Me_3SiF$ (1 equiv) was added. [i] Yield of aldol (OH form) as the minor product. [j] None of the threo isomer could be detected by $^1H$ NMR. [k] See ref 38, and the Experimental Section. [l] Not assigned. [m] Not determined. [n] Not applicable.

ketones (**26**; entry 16) and bulky alkyl ketones (**22** and **24**, entries 13 and 14) which, under conventional conditions, afford aldol products only in poor yields.[1] The regiospecific reaction of cyclobutene **28** (entry 17) to form the succinoin derivative **29** (entry 17),[24] which is sensitive to either basic or acidic conditions,[25] illustrates the mildness of the present reaction. As shown by the reactions of silyl ethers **28**, **30**, **32**, and **34**, the aldol reaction proceeds with retention of the regiochemical integrity of the starting enol silyl ethers (entries 17–19). α-Silyl ketones can also serve as

(24) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961.

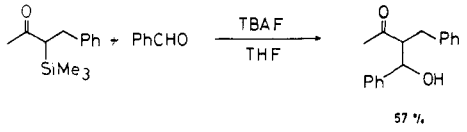
(25) Conia, J. M.; Robson, M. F. *Angew. Chem.* **1975**, *87*, 505.

Table IV. Effects of Excess 5 in the Reaction with *p*-Anisaldehyde

| 5/ArCHO | % yield[a] 11 (threo/erythro) | 36 | ArCHO |
|---|---|---|---|
| 1.1 | 58 (3:2) | 0 | 43 |
| 1.3 | 72 (3:2) | 8 | 9 |
| 2.0 | 51 | 18 | 7 |

[a] Isolated yield.

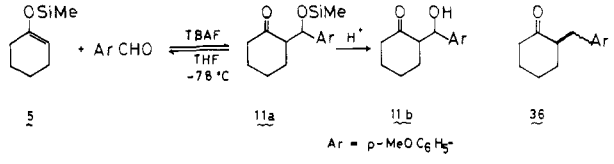
the enolate precursor of this reaction to give a diastereomeric mixture of the aldol adduct.[26]



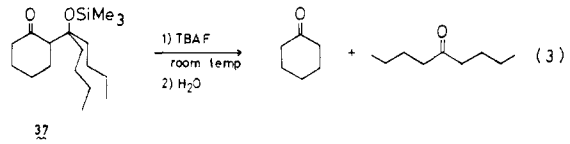

In general, aromatic aldehydes gave higher yields than the aliphatic analogues. $\alpha,\beta$-Unsaturated aldehydes yielded only 1,2-addition products, and no conjugate addition reaction was observed (entries 5 and 12, Table III).

Addition of fluorotrimethylsilane to the reaction mixture increases the yield of the aldol products (entries 14 and 15). The effect is particularly dramatic in the reaction of 1-(trimethylsiloxy)pentene (**17**) with isobutyraldehyde (entry 10). Without the fluorosilane, the reaction was so complicated as to afford the expected product in only 3% yield, but with the added fluorosilane, the yield increased to 53%. On the other hand, chlorotrimethylsilane inhibited the reaction probably by breaking the catalytic cycle.

As is evident from Table III, the product yield with benzaldehyde derivatives depends on the nature of the substituent on the aromatic ring (entries 1–4). The relatively low yield with *p*-anisaldehyde (entry 4) stands in contrast to the excellent yield with the *p*-nitro derivative (entry 1). Since the present reaction is deemed to consist of a series of mobile equilibria (vide infra), the lower yield with anisaldehyde appeared to reflect the unfavorable equilibrium toward product formation. Thus, we examined the use of excess enol silyl ether (Table IV). In fact, 1.3 equiv of **5** gave rise to a 14% increase of the yield of **11b**. A further excess of **5** caused the formation of the enone **36**.

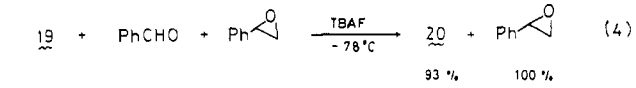



The present reaction shows very high chemoselectivity. Ketones do not serve as the electrophile of the reaction, except for such cases as benzil (Table III, entry 7). The reaction of 1-(trimethylsiloxy)-1-cyclododecene and benzophenone in the presence of TBAF (4 mol %) at −78 °C for 4 h resulted in the recovery of the unchanged starting materials in about 90% yield each. A control experiment which should shed light to the failure of this reaction was conducted. The aldol adduct **37** prepared by Mukaiyama's method[5] decomposed rapidly on exposure to TBAF (12 mol %) at room temperature to afford cyclohexanone and 5-nonanone after an aqueous workup (eq 3). The inability of the present method to couple two ketonic partners, therefore, is due to thermodynamic (with respect to the

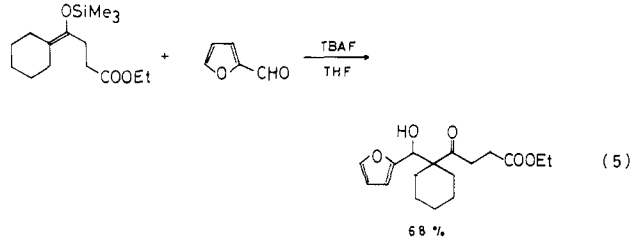



silylated compounds) as well as kinetic (at the stage of the anions) reasons (vide infra).

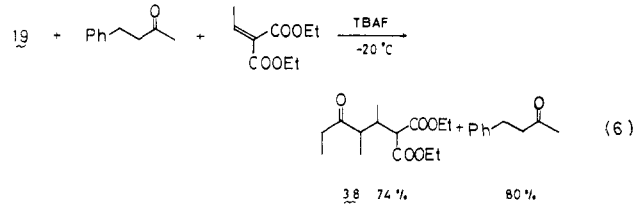
Epoxides which react with lithium enolates[27] are totally unreactive under the present conditions, and selective aldol reaction can be performed in their presence (eq 4).



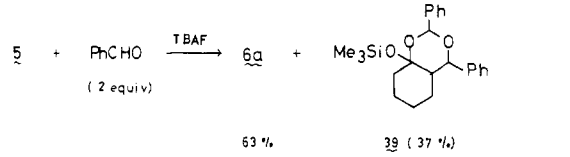

The mild reaction conditions are also illustrated by eq 5.[28] In spite of the susceptibility of a $\gamma$-keto ester to cyclization, no traces of $\gamma$-lactone derivatives were detected.




The following reaction (eq 6) further demonstrates the chemospecificity of the reaction. Fluoride anion specifically attacks the silicon atom, instead of the ketone or highly electrophilic diethyl ethylidenemalonate, to produce the Michael adduct **38**.




In some instances, the formation of 1:2 adducts in addition to the normal 1:1 adducts was observed. This appeared to have occurred when the amount of the catalyst was small (or the catalyst might have partially lost its activity?). For example, when a mixture of enol silyl ether **5** and benzaldehyde (2 equiv) was treated with 2.5 mol % of TBAF, the normal 1:1 adduct **6a** (threo and erythro)



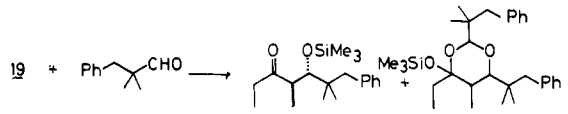

and the crystalline 1:2 adduct **39** were obtained in 63% (threo/erythro ratio of 84:16) and 37% yields (based on **5**), respectively. The assignment of the structure **39** was made on the basis of the IR, NMR, and mass spectra and the elemental composition and further ascertained by chemical transformation. Treatment of the recrystallized material with aqueous HCl in methanol gave back the erythro aldol **6b**, benzaldehyde, and its dimethyl acetal in a ratio of 1.0:0.2:0.5.

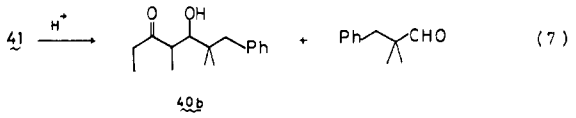
(26) See ref 11 in: Kuwajima, I.; Inoue, T.; Sato, T. *Tetrahedron Lett.* **1978**, 4887.

(27) Hudrlik, P. F.; Wan, C.-N. *J. Org. Chem.* **1975**, *40*, 2963.

(28) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *J. Org. Chem.* **1977**, *42*, 4166.

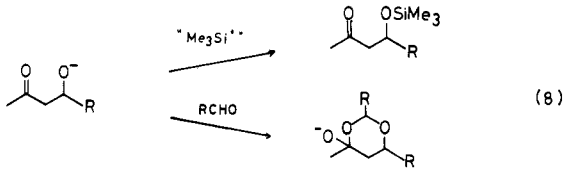
The reaction of a sterically hindered aldehyde, 2,2-dimethyl-3-phenylpropanal (1 equiv) similarly gave a mixture of the threo aldol **40a** and the 1:2 adduct **41**, in 11% and





37% yields, respectively. Treatment of **41** with aqueous HCl in methanol gave a mixture of the 1:1 aldol adduct **40b** (threo/erythro ratio of 11:9) and the starting aldehyde (eq 7), in 79% and 67% isolated yields, respectively.

The 1:2 adduct formation probably occurred when the silylating agent in the system (e.g., fluorotrimethylsilane) is less effective in trapping the aldol anion than the aldehyde (eq 8) and was avoided simply by using a relatively



large amount of the catalyst (5–20 mol %) or by the addition of fluorotrimethylsilane to the system. Moreover, the use of excess aldehyde, followed by acid hydrolysis, would circumvent the problem (cf. eq 7), since the 1:2 adduct smoothly regenerates the 1:1 adduct on hydrolysis.

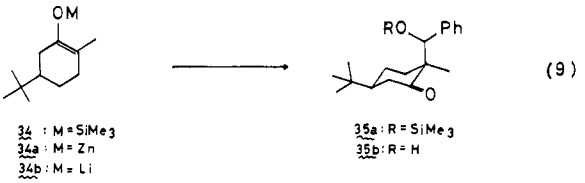
**Stereochemistry.** Owing to the recent intensive studies on enolate chemistry, many of the problems associated with the controlling of the regioselectivity of the reaction have been resolved.[1b,29] The problem of the stereoselectivity, however, has been less explored. Significant effects of the cationic portion of the enolate on the stereochemistry of the aldol reaction had been expected, yet, until very recently, there have been only a few studies which actually revealed such effects.[1b]

Two of the stereochemical problems in aldol reactions are discussed here. One is concerned with the position $\alpha$ to the carbonyl group and the other with the relative stereochemistry between the $\alpha$- and $\beta$-positions.

Axial–equatorial selectivity, which must be considered when a substituent is added to a cyclohexane ring, is one of the most fundamental aspects of the stereochemical problems and is considered to depend on two factors: steric interaction and stereoelectronic control. Although evaluation of the former is rather straightforward and well precedented, e.g., 1,3-diaxial interactions, that of the latter appeared worthy of further investigation. We examined the aldol reaction of 5-*tert*-butyl-2-methylcyclohexanone, which has previously been studied in detail by House.[9a,30]

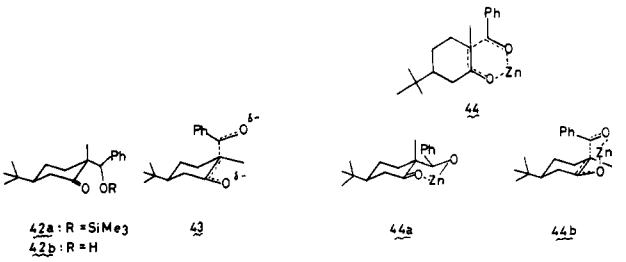
This ketone represents a nice case of a sterically unhindered, conformationally stable system, in which the stereochemistry of the C-2-alkylated product would directly reflect the kinetic result. The examination of this system has revealed a most intriguing characteristic of the present reaction.

Thus, we treated a mixture of the enol silyl ether **34** and benzaldehyde with TBAF at −35 °C for 1.5 h and found the exclusive formation of the stereoisomers (**35a**, threo/erythro ratio of 64:36) that bear the newly introduced substituent in the axial position (eq 9). This high



stereoselectivity was observed under a variety of conditions, although the threo–erythro selectivity was always low.

Evidently, the attack of the aldehyde on the six-membered ring occurs exclusively from the stereoelectronically favored axial direction via the transition state **43**. Such



a rigorous stereoelectronic control has not been reported for the introduction of an $\alpha$ substituent to a simple unhindered cyclohexanone ring. In a similar case, the reaction of zinc enolate **34a** gave ca. 40% of the equatorial isomer **35b**, although it did yield the less stable **42b** as the major product.[9a] The large drop of the selectivity in the zinc case, presumably a thermodynamically controlled process, is considered to reflect the stability of the chelated transition state, rather loosely defined as **44**. The chelated bicyclic structure should stabilize the "trans-fused" product **44a** against the stereoelectronic requirements of the cyclohexene ring structure which favors the "cis-fused" transition state **44b**, leading to the "equatorially attacked" product. On the other hand, the stereochemistry in the TBAF catalysis is only subject to the stereoelectronic requirements of the cyclohexene ring.[32]

The contrast between the extremely high axial (kinetic) selectivity and the apparent lack of the threo–erythro selectivity in the fluoride-catalyzed reaction of **34** is noteworthy, the latter indicating the occurrence of equilibration at the aldol anion stage. Consequently, the assumption that the lack of the chelation in a transition state such as **43** renders the path leading to the *aldol anion* corresponding to **42a** energetically unavailable accommodates the very slow isomerization of **35a** to the *silyl* aldol **42a** in spite of the rather strained nature of **35a**. A related situation is found in the aldol reaction between an $\alpha$-substituted enolate anion and an $\alpha$-substituted aldehyde with respect to "internal" and "relative" asymmetric induction among positions $\alpha$, $\beta$, and $\gamma$ of the resulting aldol adduct.[12a]

(29) Review: d'Angelo, J. *Tetrahedron* **1977**, *33*, 2977.
(30) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 1000.
(31) (a) Neilsen, A. T. *J. Org. Chem.* **1965**, *30*, 3650. (b) Stiles, M.; Winkler, R. R.; Chang, Y.; Traylor, L. *J. Am. Chem. Soc.* **1964**, *86*, 3337. (c) Zimmerman, H. E.; Traxler, M. D. *Ibid.* **1957**, *79*, 1920. (d) Dubois, J. E.; Duois, M. *Tetrahedron Lett.* **1967**, 4215; *Chem. Commun.* **1968**, 1567. (e) Dubois, J. E.; Fellmann, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1972**, *274*, 1307. (f) Reviews on the stereochemistry of the aldol reaction: Heathcock, C. H. "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E. Eds.; Elsevier: Amsterdam, 1982; Vol. 2, Chapter 4. Evans, D. A. *Top. Stereochem.* **1982**, *13*, 1.

(32) The same type of transition state, i.e., "extended" vs. chelated, explains the acyclic stereoselection of naked enolates.[34]

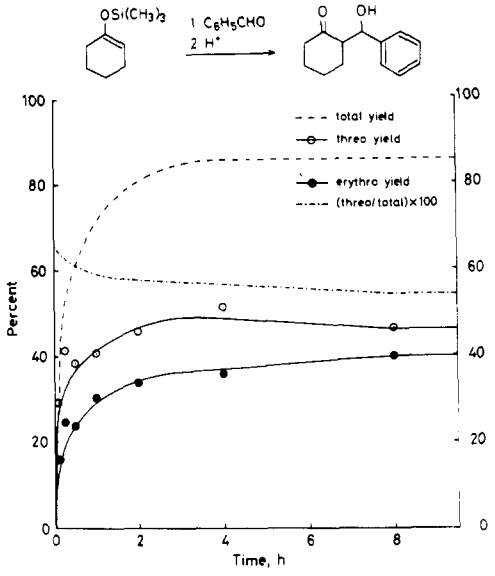



**Figure 1.** Time dependency of the reaction of **5**.

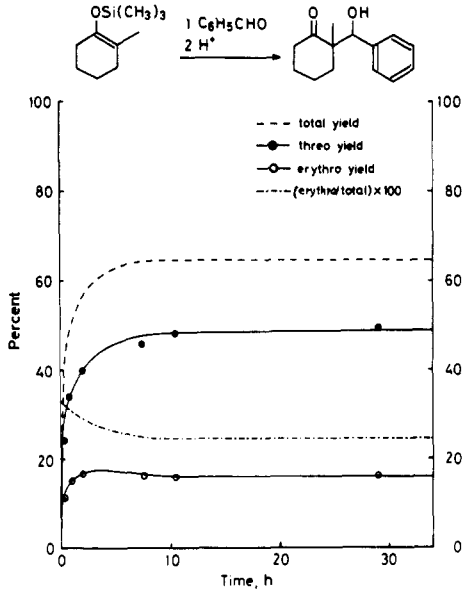



**Figure 2.** Time dependency of the reaction of **30**.

Interestingly, no great effect of the countercation was observed in alkylation reactions. Alkylation of **34** with $CD_3I$ with the aid of BTAF proceeded with 79% axial attack of the alkylating agent,[19b] while that of the lithium enolate **34b** showed 83% axial selectivity.[30]

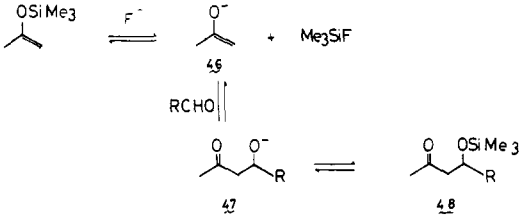
The threo–erythro selection of aldol reactions[31] is subject to the change of the countercation. House reported that the (thermodynamic) threo/erythro ratio in the aldol reaction between cyclohexanone and benzaldehyde varies from 1:1 with sodium or lithium enolate to 5:1 with zinc enolate.[9a] The $TiCl_4$-mediated reaction of **5** and benzaldehyde gave a ratio of 3:1,[5] while the trimethylsilyl triflate mediated one with acetals gave the erythro isomer preferentially.[6] Boron enolates have been shown to be highly threo selective in this reaction.[11b]

In the present TBAF-catalyzed reaction, the diastereomeric ratio in the reaction of **5** and benzaldehyde proved to be time dependent. The ratio of *threo*-**6b** to *erythro*-**6b** changed gradually from 65:35 (5 min, 45% yield) to a final equilibrium of 54:46 (8 h, 86%) (Figure 1). When the reaction of **30** and benzaldehyde was monitored, the ratio of *threo*-**31** to *erythro*-**31**[33] was found to vary from 67:33 (4 min, 21%) to 74:26 (10.5 h, 64%) (Figure 2).

The ready reversibility of the present aldol reaction (vide supra), as well as the general absence of the elimination products (enones) in the reaction mixture, suggests that the time dependency of the diastereomeric ratio is caused by a retroaldol process instead of a less likely enolization process (impossible for **31**). The diastereomeric ratio, however, depends on the precise reaction conditions: the reaction of **17** and isobutyraldehyde in the presence of TBAF and fluorotrimethylsilane gave the adduct **18** as a single erythro isomer. The function of the fluorosilane is in consonance with the mechanistic scheme (vide infra) and recently culminated in the discovery of a new stereoselective aldol reaction.[34]

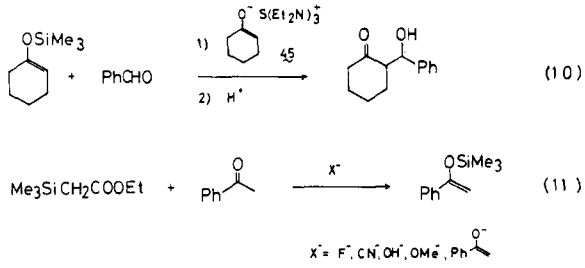
**Reaction Course.** The unique characteristics of the new aldol reaction stem from the nature of the reactive species as well as the catalytic mechanism. No reaction was observed either when an aldehyde was treated with an enol silyl ether alone or when a ketone, an aldehyde,

**Scheme II**




and the fluoride anion were mixed together (eq 2). The dramatic effects of added fluorotrimethylsilane in an (apparently troublesome) aldol reaction of cyclopentanone as well as its ability to prevent 1:2 adduct formation (eq 8) is revealing. It is thus evident that tetraalkylammonium fluoride and fluorotrimethylsilane play important roles in the reaction.

On the other hand, neither the fluoride anion nor the tetraalkylammonium cation is essential for this type of catalysis (cf. Table I), though this combination represents the only system of high practical value. For instance, the naked enolate anion **45** initiates the reaction to give the adduct **6a** in moderate yield (eq 10).[34] The related re-




action of ethyl (trimethylsilyl)acetate[35] is catalyzed by naked methoxide, cyanide, and an enolate anion as well as fluoride anion with equal ease (eq 11).[20a]

The mechanism of the fluoride-catalyzed reaction may be depicted as a series of very mobile equilibria shown in Scheme II. Interaction of the fluoride anion with an enol silyl ether produces a naked enolate anion **46** which un-

(33) The original assignment of *threo*- and *erythro*-**31** reported by Mukaiyama[5] was reversed by X-ray analysis: private communication to E.N. from Professor P. L. Stotter, San Antonio, TX.

(34) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106.

(35) (a) Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2346. (b) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 2079.

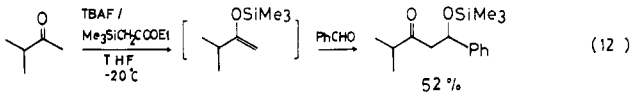
dergoes (reversible) addition to an aldehyde to give the aldol anion **47**. This, in turn, is trapped by fluorotrimethylsilane produced in the first step. However, as eq 10 and 11 indicate, an autocatalytic mechanism[20] evidently operates in part.

The reversibility of the overall reaction is readily seen in the rapid decomposition of the silyl aldol **37** (eq 3). On the other hand, the very fast threo–erythro equilibration observed before the completion of the reaction (Figures 1 and 2) implies the ready equilibration at the anionic stage; namely, the aldol anion **47** formed at the initial stage goes partly to the product **48** and partly falls back to the starting enolate anion **46**. This situation is also observed in the reaction of **34** (eq 9). The formation of the apparently less stable axial adduct **35a** reflects the kinetic selectivity of the enolate anion stage, whereas the (equilibrated) threo–erythro ratio appears to be determined by the thermodynamic factors among either of the diastereomers of the aldol anion **47**.

In this mechanistic context, the effects of added fluorosilane to suppress two undesirable side reactions are rationalized by considering the effective trapping of the aldol anion **47** with an increased amount of fluorosilane in the system: the prevension of the 1:2 adduct formation in competition with formation of an aldehyde (eq 8) and the yield enhancement in the reaction of cyclopentanone against the retroaldol reaction or other base-catalyzed reactions. The exclusive formation of erythro **18** in the reaction of **17** can also be attributed to the rapid trapping of **47** with the added fluorosilane, which allows the aldol anion **47** to retain the initial kinetic stereochemistry.[34]

## Conclusion

The present aldol reaction represents one of the basic reactions in a series of tetraalkylammonium fluoride aided reactions of silylated enols which proceed under very mild conditions.[19,35] Combination of the aldol reaction and the mild silylation procedure[35] has realized a cross-aldol reaction without recourse to either strongly basic or acidic reagents. For example, the reaction of isopropyl methyl ketone and benzaldehyde was performed in a single pot without isolating the intermediate (eq 12).




(12)

Another point of interest demonstrated by the present reaction is the possibility of controlling the stereochemical course of the reaction. Striking effects of the countercation both in axial–equatorial and in threo–erythro selection suggested similar possibilities in the reactions of other anionic species, which are now gradually being demonstrated to be true.

## Experimental Section

**General Methods.** Melting points, determined in glass capillaries, and boiling points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi EPI-G3 or JASCO DS-402G spectrometer; absorptions are reported in reciprocal centimeters. Proton nuclear magnetic resonance spectra ($^1$H NMR) were obtained on a Varian Associates Model T-60 or HA-100-D or a JEOLCO Model JNM-C-60H spectrometer; chemical shifts ($\delta$) are expressed in parts per million downfield from internal tetramethylsilane. Analytical gas–liquid chromatography (GLC) was performed on a Hitachi 063 instrument with a flame-ionization detector and nitrogen carrier gas (1.0–1.3 kg/cm$^2$).

Preparative thin-layer chromatography (TLC) was carried out on glass plates (20 × 20 cm) coated with Merck silica gel PF 254 (1 mm thick). Column chromatography was performed on Wakogel C-200 silica gel or Merck Kieselgel 60. Mass spectra (70 eV) were determined on a Hitachi RMU-6C or RMU-7M spectrometer. Microanalyses were performed with a Perkin-Elmer 240 at the Microanalytical Laboratory, Tokyo Institute of Technology.

Reactions involving air- or moisture-sensitive compounds were conducted in appropriate round-bottomed flasks with magnetic stirring bars under nitrogen or argon. Bulb-to-bulb distillation was performed with a Büchi Kugelrohr apparatus.

Ether, tetrahydrofuran (THF), and dimethoxyethane were distilled from sodium/benzophenone ketyl immediately before use. Acetonitrile and methylene chloride were distilled successively from $P_2O_5$ and $K_2CO_3$. Benzene was distilled from calcium hydride. Dimethylformamide and dimethyl sulfoxide were distilled under reduced pressure from calcium hydride.

**Materials.** Enol silyl ethers **5** and **17** were prepared either by House's method A[4b] or by the silylation procedure with ethyl (trimethylsilyl)acetate.[35] Enol silyl ethers **8**, **19**, **22**, **24**, and **26** were prepared according to House's method A and **32** by method B.[4b] Enol silyl ether **30** was prepared from the lithium enolate which was generated from the corresponding enol acetate.[36] The isomeric silyl enol ethers **30** and **32** were 98% pure as judged by GLC (5% XE-30 on Chromosorb P(AW), 1 m × 3 mm, 45 °C). Enol silyl ether **34** was prepared from the corresponding enol ester.[30] Enol silyl ether **28** was prepared by acyloin condensation of diethyl succinate[37] and was found to be isomerically pure.

Ketones were distilled before use. Aldehydes were washed with aqueous $NaHCO_3$, dried, and distilled before use. 2,2-Dimethyl-3-phenylpropanal was prepared by Stork's procedure.[43] Inorganic fluorides were dried over $P_2O_5$ (100 °C, 0.03 mm) overnight and kept in a desiccator. Tetrabutylammonium fluoride (TBAF), either commercially available as the trihydrate (Fluka) or prepared as previously described,[23b,35b] was dried over $P_2O_5$ (30–40 °C, 0.5 mm, 15 h) and stored in a desiccator. Other tetraalkylammonium fluorides were prepared similarly. Benzyltrimethylammonium fluoride (BTAF) was prepared and dried as previously described.[19]

**Aldol Reaction.** The reaction was carried out in a round-bottomed flask with a three-way stopcock or in a simple glass-sealed tube under an inert gas (argon or nitrogen) atmosphere. Solid materials were placed in the reaction vessel either in a drybox or in a polyethylene drybag, and liquid reagents were introduced with a hypodermic syringe through a rubber septum. The filtration procedure was performed with a pad of Hyflo Super Cell or Celite 545, and concentration of organic solutions was usually achieved on a rotary evaporator with a water aspirator. The aldol products were obtained, when possible, as a mixture of the threo and erythro isomers. The stereochemical assignment as well as the determination of the product ratio was made on the basis of the easily recognizable NMR signals due to the CHOH proton,[5,9a] assuming an internally hydrogen-bonded structure of an aldol.[38] Table V summarizes the crucial NMR data of the structurally defined aldols.

**2-(Hydroxyphenylmethyl)cyclohexanone (6b). (A) With Tetrabutylammonium Fluoride (TBAF) as a Catalyst. General Procedure and Workup Methods A and B.** A solution of TBAF (16 mg, 0.06 mmol) in 2 mL of THF was placed in a glass tube and kept at −78 °C under argon atmosphere. To this solution was added benzaldehyde (120 mg, 1.1 mmol) and 1-(trimethylsiloxy)cyclohexene (**5**; 170 mg, 1.00 mmol). The resulting mixture was stirred at −78 °C for 3.5 h, quenched by addition of water, warmed to room temperature, and extracted with ether repeatedly. The organic extracts were combined, dried, and concentrated in vacuo (workup method A) to leave an oil (266 mg), which was subjected to bulb-to-bulb distillation (bath tem-

(36) Gall, M.; House, H. O. *Org. Synth.* **1972**, *52*, 39.
(37) (a) Ruhlmann, K. *Synthesis* **1971**, 236. (b) Bloomfield, J. J.; Nelke, J. M. *Org. Synth.* **1977**, *57*, 1.
(38) (a) For the recent $^{13}$C NMR-based assignment and exceptions for this hypothesis: Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294. (b) Canceill, J.; Basselier, J.-J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 1024. (c) Canseill, J.; Jacques, J. *Ibid.* **1970**, 2180. (d) Mulzer, J.; Zippel, J.; Bruntrup, G.; Segner, J.; Finke, J. *Liebigs Ann. Chem.* **1980**, 1108. We thank a referee for pointing out the possible reversal of the assignment of the diastereomers of **23** by calling our attention to ref 38b–d.

Table V. NMR Signals of CHOH Protons of Aldols

| compd | δ(CHOH) | J, Hz | solvent |
|---|---|---|---|
| **10** threo | 4.93 | 8 | $CDCl_3$ |
| erythro | 4.70 | ~1 | $CDCl_3$ |
| **11** threo | 4.73 | 9 | $CDCl_3$ |
| erythro | 5.32 | 3 | $CDCl_3$ |
| **15** threo | 4.48 | 8 | $CCl_4$ |
| erythro | 5.09 | 3.8 | $CCl_4$ |
| **16** threo | 4.70 | 8 | $CCl_4$ |
| erythro | 4.09 | 3 | $CCl_4$ |
| **18** threo | 3.62 | 2 | $CCl_4$ |
| **23** threo[a] | 4.83 | 8 | $CCl_4$ |
| erythro[a] | 4.85 | 4 | $CCl_4$ |
| **31** threo | 4.85 | | $CCl_4$ |
| erythro | 4.93 | | $CCl_4$ |
| **33** equatorial-threo | 4.66 | 8 | $CCl_4$ |
| axial-threo | 4.77 | 8 | $CCl_4$ |
| equatorial-erythro | 5.18 | 3 | $CCl_4$ |
| axial-erythro | 5.25 | 2 | $CCl_4$ |
| **35** axial-threo | 5.08 | | $CCl_4$ |
| axial-erythro | 4.81 | | $CCl_4$ |
| **40** threo | 3.57 | 3 | $CCl_4$ |
| erythro | 3.50 | 2 | $CCl_4$ |

[a] The applicability of the assigning protocol in the text (by J value) is rather tenuous, and the assignment may need to be reversed (see ref 38).

perature 160–180 °C, 0.03 mm), giving the title aldol **6b** (170 mg, 84%) as a 3:2 mixture of the threo and erythro isomers (Table VI). In the $^1H$ NMR spectrum, the erythro isomer showed the benzylic signal at δ 5.30, while the threo isomer exhibited the corresponding signal at δ 4.66.[5a,9a] The structure was established by comparison with an authentic sample.[5a]

Dilution of the reaction mixture, prior to the aqueous workup, with a large amount (20 mL) of hexane, followed by treatment with water, drying (workup method B), and distillation (bath temperature 105–140 °C, 0.05 mm) gave the corresponding trimethylsilyl ether **6a** (208 mg, 75% yield).

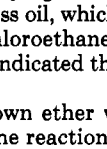
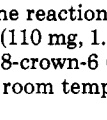
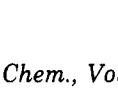
**(B) With Benzyltrimethylammonium Fluoride (BTAF) as a Catalyst.** To a suspension of BTAF (56 mg, 0.33 mmol) in 4 mL of THF at −40 °C was added a solution of **5** (169 mg, 0.99 mmol) and benzaldehyde (105 mg, 0.99 mmol) in 2 mL of THF. The reaction mixture was stirred for 2 h and filtered after dilution with 10 mL of hexane. The crude product (277 mg) was separated into three fractions on TLC purification. The fractions consisted of the silyl aldol **6a** (107 mg, 39% yield), the enone **7** (26 mg, 14%), and the aldol **6b** (54 mg, 27%). The BTAF-catalyzed reactions carried out under a variety of conditions (solvent THF, THF–dimethyl sulfoxide, dimethoxyethane; temperature −78 to −20 °C; BTAF, 0.1–1.0 equiv) gave the desired aldol products in 33–66% combined yield and the enone **7** in 4–19% yield.

**(C) With Tetraethylammonium Fluoride as Catalyst.** A solution of **5** (170 mg, 1.00 mmol) and benzaldehyde (120 mg, 1.1 mmol) in 1 mL of THF was added to 2 mL of THF containing tetraethylammonium fluoride (6 mg, 0.04 mmol) at −78 °C under argon. The mixture was maintained at −25 °C for 16 h and then treated with water and ether. The ethereal layer was dried, concentrated, and distilled (bath temperature 160–180 °C, 0.2 mm) to give **6b** (130 mg, 64% yield) as a colorless oil.

**(D) With Inorganic Fluorides.** The following procedure is illustrative. A mixture of **5** (170 mg, 1.00 mmol), benzaldehyde (120 mg, 1.1 mmol), and KF (65 mg, 1.1 mmol) in 2 mL of acetonitrile was stirred at 60 °C for 18 h. After cooling to room temperature, the mixture was quenched with water and extracted with ether. Drying and concentration of the extracts afforded a crude colorless oil, which was analyzed by $^1H$ NMR with added 1,1,2,2-tetrachloroethane as an internal standard (53 μL, 0.50 mmol) which indicated the formation of the aldol adduct in 41% yield.

When a crown ether was added, only mild conditions were required for the reaction. A mixture of **5** (170 mg, 1.00 mmol), benzaldehyde (110 mg, 1.10 mmol)8 KF (10 mg, 0.17 mmol), and dicyclohexyl-18-crown-6 (6 mg, 0.016 mmol) in 2 mL of benzene was stirred at room temperature for 16 h and quenched by the

Table VI. Aldol Reaction

| enol silyl ether | amt, mg (mmol) | aldehyde (mg, mmol) | TBAF, mg (mmol) | temp, °C (time, h) | aldol, mg (% yield) [β-siloxy ketone] | threo/erythro ratio | purification | workup |
|---|---|---|---|---|---|---|---|---|
|  **5** | 340 (2.00) | cinnamaldehyde (300, 2.30) | 52 (0.2) | −78 (4) | (51) [305] | *a* | dist, TLC (hex/AcOEt) | B |
| | 229 (1.35) | 3-phenylpropanal (164, 1.35) | 16 (0.06) | −30 (2) | 104 (37) | *a* | TLC (hex/$Et_2O$) | C |
| | 170 (1.00) | benzil (232, 1.10) | 22 (0.09) | −78 (5), −25 (20) | 96[b] (31) | *a* | dist, column (hex/$Et_2O$) | A |
|  **8** | 184 (1.00) | furfural (110, 1.10) | 15 (0.06) | −78 (3), −25 (22) | 197 (95) | 1:2 | dist, TLC (hex/$Et_2O$) | D |
| | 184 (1.00) | benzaldehyde (120, 1.10) | 28 (0.11) | −78 (6.5) | 174 (80) | 1:2 | dist, TLC (hex/$Et_2O$) | D |
|  **19** | 200 (1.26) | benzaldehyde (122, 1.15) | 15 (0.06) | −78 (5) | (70) [211] | *a* | dist | B |
| | 393 (2.49) | (*E*)-2-hexenal (188, 1.91) | 25 (0.1) | −78 (24) | 170 (48) | *a* | TLC (hex/$Et_2O$) | C |
|  **22** | 214 (1.00) | benzaldehyde (120, 1.10) | 15 (0.06) | −78 (3), −25 (22) | 164 (59) | 3:5 | dist, TLC (hex/AcOEt) | A |

[a] Not determined. [b] Recovery of benzil (118 mg, 50%).

addition of water. The mixture was extracted with ether and the ethereal extract was dried and concentrated to afford an oil (267 mg). NMR analysis of this oil indicated the production of the aldol adduct in 50% yield.

Other reactions listed in Table I were carried out in an analogous manner.

**BTAF-Catalyzed Reactions of 1-(Trimethylsiloxy)cycloheptene (8) in Various Solvents.** The aldol reaction of 8 and benzaldehyde was examined in various solvents, the results being summarized in Table II. Thus 1-(trimethylsiloxy)cycloheptene (180 mg, 0.98 mmol) and benzaldehyde (124 mg, 1.2 mmol) were added to a solution of BTAF (25 mg, 0.10 mmol) in 3 mL of the stated solvent. The reaction mixture was maintained at the indicated conditions, poured into 20 mL of hexane, and then treated with water. The organic layer was dried, concentrated, and analyzed by NMR with added 1,1,2,2-tetrachloroethane as an internal standard (52 μL, 0.49 mmol).

**2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (10) by Workup Method C.** A solution of *p*-nitrobenzaldehyde (625 mg, 4.14 mmol) and **5** (774 mg, 4.55 mmol) in 5 mL of THF was added to a cooled (−78 °C) suspension of TBAF (54 mg, 0.21 mmol) in 0.5 mL of THF. After being stirred for 3 h at that temperature and at −40 °C for an additional hour, the reaction mixture was quenched by adding 4 mL of $AcOH/H_2O$ and stirred overnight at room temperature. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with ether (3 × 10 mL). After being dried and concentrated in vacuo, the ethereal extract afforded a yellow oil (1.08 g), which was separated by column chromatography (50 g of silica gel; hexane/ether) into three solid materials, A, B, and then C.

A was identified by spectral data and TLC as pure *p*-nitrobenzaldehyde (26 mg, 4%).

B was the pure erythro isomer of **10** obtained as yellow crystals: 398 mg (36%); mp 120–120.5 °C (benzene); IR (KBr) 3495 (br, OH), 1705 (vs, C=O); $^1H$ NMR ($CDCl_3$) 0.80–2.85 (m, 9 H, $CH_2CHO$=O), 3.3 (d, $J$ = 3 Hz, 1 H, OH; this signal disappeared on $D_2O$ treatment), 4.70 (m, 1 H, CHOH; this signal became a br s on $D_2O$ treatment), 7.46 (d, $J$ = 9 Hz, 2 H, aromatic protons meta to nitro group), 8.14 (d, $J$ = 9.0 Hz, 2 H, aromatic protons ortho to nitro group). Anal. ($C_{13}H_{15}NO_4$) C, H, N.

C was a 1:1 diastereomeric mixture of the isomers of **10** (548 mg, 56%; the isomer ratio was based on the $^1H$ NMR spectrum of the product). Thus, the threo–erythro selectivity of the reaction was 2:5. Further purification by chromatography and recrystallization afforded the pure threo isomer as yellow crystals: mp 146–147 °C (benzene); IR (KBr) 3500 (s, OH), 1695 (vs, C=O); $^1H$ NMR ($CDCl_3$) 1.0–3.1 (m, 9 H, $CH_2$, CHC=O), 3.95 (d, $J$ = 4 Hz, 1 H, OH), 4.93 (dd, $J$ = 4, 8 Hz, 1 H, CHOH), 7.50 (d, $J$ = 9 Hz, 2 H, aromatic protons meta to nitro group), 8.20 (d, $J$ = 9 Hz, aromatic protons ortho to nitro group). Anal. ($C_{13}H_{15}NO_4$) C, H, N.

**2-(1-Hydroxy-2-methylpropyl)cyclopentanone (18) by Workup Method D.** To a solution of 1-(trimethylsiloxy)cyclopentene (**17**; 1.50 g, 9.60 mmol), isobutyraldehyde (744 mg, 12 mmol), and fluorotrimethylsilane[39] (1.92 g, 24 mmol) in THF (30 mL) was added a solution of TBAF (262 mg, 1.0 mmol) in 2 mL of THF at −78 °C. The mixture was warmed to −30 °C, kept at this temperature for 14 h, and poured into 200 mL of hexane. The hexane solution was washed with water, dried, evaporated, and distilled to give 1.41 g of an oil (bath temperature 100–180 °C, 20 mm). This oily product was dissolved in 5 mL of 1:10 1 N $HCl/CH_3OH$ and stirred at room temperature for 10 min. The mixture was then diluted with 1:1 hexane/ether and washed with water. The organic layer was dried and concentrated, giving a crude aldol product (962 mg, 80% pure). This oil (544 mg) was chromatographed on a silica gel column (50 g, 1:1 hexane/ethyl acetate) to give the pure erythro aldol product (432 mg, 52% yield), no threo isomer being detected. The erythro aldol exhibited the following spectral properties: IR ($CCl_4$) 3670 (w, OH), 3527 (s, OH), 1732 (vs, C=O); $^1H$ NMR ($CCl_4$) 0.87 (d, 3 H, $J$ = 7 Hz, $CH_3$), 0.99 (d, 3 H, $J$ = 7 Hz, $CH_3$), 1.2–2.3 (m, 8 H, $CH_2$, CH), 2.63 (d, 1 H, $J$ = 3 Hz; OH disappeared on treatment with $D_2O$), 3.62 (br d, 1 H, $J$ = 8 Hz, CHOH; dd with added $D_2O$, $J$ = 8 and 2 Hz); mass spectrum, $m/e$ 156 ($M^+$), 148 ($M^+$ − 18), 113 ($M^+$ − 43), 83 ($M^+$ − 73).

**2-[Hydroxy(4-methoxyphenyl)methyl]cyclohexanone (11).** A solution of *p*-anisaldehyde (135 mg, 1.00 mmol) and **5** (220 mg, 1.30 mmol) in 1 mL of THF was added to a suspension of TBAF (13 mg, 0.05 mmol) in 0.5 mL of THF at −78 °C. After being stirred for 4 h at that temperature, the reaction mixture was treated with 1 mL of $AcOH/H_2O$ (1:2) and stirred overnight at room temperature. The mixture was neutralized with aqueous $NaHCO_3$ and extracted with ether (3 × 3 mL). The extract was dried and concentrated in vacuo to leave a yellow oil (246 mg). Preparative TLC (hexane/ether) afforded three fractions: A, B, and then C.

A was 2-[(4-methoxyphenyl)methylene]cyclohexanone (11 mg, 8%): IR (neat) 1685 (vs, C=O), 1610 (vs, C=C); $^1H$ NMR ($CCl_4$) 1.30–2.06 (m, 9 H, CH, CHC=O), 3.76 (s, 3 H, $CH_3O$), 6.71 (d, $J$ = 9 Hz, 2 H, aromatic protons ortho to methoxy group), 7.12–7.50 (m, 3 H, aromatic protons meta to methoxy group and an olefinic proton).

B was identified as pure *p*-anisaldehyde (20 mg, 9% recovery).

C was a diastereomeric mixture of the tital aldol **11** (169 mg, 72%). Examination of the relative intensity of the NMR signals assigned to the benzylic protons (vide infra) indicated the threo–erythro ratio to be 62:38. This mixture was further chromatographed on a silica gel column to give the pure isomers, among which the erythro isomer eluted first (hexane/ether).

Erythro isomer: mp 115.5–117 °C (hexane/benzene); IR (KBr) 3430 (s, OH), 1695 (vs, C=O); $^1H$ NMR ($CDCl_3$) 1.3–2.8 (m, 9 H, $CH_2$, CHO=O), 3.00 (d, 1 H, $J$ = 3 Hz, OH, disappeared on $D_2O$ treatment), 3.79 (s, 3 H, $CH_3O$), 5.32 (m, 1 H, CHO; this signal became a d, $J$ = 3 Hz, on $D_2O$ treatment), 6.85 (unresolved d, 2 H, $J$ = 9 Hz, aromatic protons ortho to methoxy group), 7.05–7.30 (m, 2 H, aromatic protons meta to methoxy group). Anal. ($C_{14}H_{18}O_3$) C, H.

Threo isomer: mp 75–76 °C (hexane/benzene); IR (KBr) 3430 (s, OH), 1705 (vs, C=O); $^1H$ NMR ($CDCl_3$) 1.1–2.8 (m, 9 H, $CH_2$, CHC=O), 3.80 (s, 3 H, $CH_3O$), 3.87 (d, $J$ = 3 Hz, 1 H, OH), 4.73 (dd, $J$ = 3, 9 Hz, 1 H, CHO), 6.83 (unresolved d, $J$ = 9 Hz, 2 H, aromatic protons ortho to methoxy group), 7.05–7.30 (m, 2 H, aromatic protons meta to methoxy group). Anal. ($C_{14}H_{18}O_3$) C, H.

**4,4-Dimethyl-1-hydroxy-1-phenyl-3-pentanone (25b).** A solution of 3,3-dimethyl-2-(trimethylsiloxy)-1-butene (**24**; 172 mg, 1.00 mmol), benzaldehyde (120 mg, 1.1 mmol), and TBAF (17 mg, 0.065 mmol) in 3 mL of THF was allowed to stand at −78 °C for 2.5 h, quenched with water, and extracted with ether. The extracts were dried and concentrated to leave a crude oil (188 mg). Bulb-to-bulb distillation (bath temperature 80–170 °C, 0.03 mm) afforded the tital aldol: 86 mg (42%); IR ($CCl_4$) 3485 (s, OH), 1688 (vs, C=O); $^1H$ NMR ($CCl_4$) 1.11 (s, 9 H, $CH_3$), 2.76 (d, 2 H, $J$ = 6 Hz, $CH_2$), 5.03 (t, 1 H, $J$ = 6 Hz, CH), 7.25 (m, 5 H, $C_6H_5$); mass spectrum, $m/e$ 188 ($M^+$ − 18), 160 ($M^+$ − 46), 149 ($M^+$ − 57). The structure was identified by comparison with the authentic sample.[7a]

To a THF solution (2 mL) of TBAF (38 mg, 0.15 mmol) and fluorotrimethylsilane (168 mg, 2.0 mmol) cooled at −78 °C was added a mixture of **24** (345 mg, 2.00 mmol) and benzaldehyde (210 mg, 2.00 mmol) in 3 mL of THF. The solution was stirred at −25 °C for 16 h and then treated with water and ether. The organic layer was dried, concentrated, and distilled to afford benzaldehyde (116 mg; bath temperature <70 °C, 0.03 mm) and a mixture of the aldol adduct **25b** and its trimethylsilyl ether **25a** (10% and 54% yield, respectively): (337 mg; bath temperature 120–150 °C 0.03 mm). Treatment of the latter with 2.4 mL of 1.2 N $HCl/CH_3OH$ (1:7) mixture at room temperature for 2 h followed by extraction with ether and concentration gave **25b** (281 mg, 50% yield).

**2-[Phenyl(trimethylsiloxy)methyl]-2-(trimethylsiloxy)-cyclobutanone (29).** To a suspension of TBAF (0.46 g, 1.76 mmol) in 4 mL of THF at −78 °C was added dropwise a solution of 1,2-bis(trimethylsiloxy)cyclobutene (**28**; 2.76 g, 12 mmol) and benzaldehyde (1.06 g, 10 mmol) in 4 mL of THF. The yellow mixture was stirred for 3.5 h at −78 °C and then at −30 °C for 30 min. The reaction mixture was poured into 50 mL of hexane. After the mixture was washed with water and with aqueous NaCl and concentrated, a pale yellow oil (3.15 g) was obtained. Pu-

(39) Schmidt, M.; Schmidbaur, H. *Chem. Ber.* **1961**, *94*, 2446.

rification by column chromatography (70 g of silica gel, 5% ether in hexane) gave the title cyclobutanone **29**: 2.28 g (68%); bp 95–105 °C (bath temperature; 0.1 mm); IR (neat) 1793 (s), 1255 (w), 1100 (m), 848 (s); $^1$H NMR ($CCl_4$) 0.07 and 0.12 (2 s, 18 H, $CH_3Si$), 1.5–3.0 (m, 4 H, ring protons), 4.65 (s, 0.33 H) and 4.68 (s, 0.67 H, $CHC_6H_5$), 7.24 and 7.27 (2 s, 5 H, $C_6H_5$); mass spectrum, $m/e$ 336 ($M^+$), 321, 147, 73.

Elution with 50% ether in hexane then gave partially desilylated products (0.30 g, 11%) which showed IR bands at 3420, 1788, 1251, 1097, 1070, 87, 841, 788, and 757 $cm^{-1}$ and a diastereomeric benzylic proton at $\delta$ 4.66 and 4.68 as 2 s two singlets in the NMR ($CCl_4$) spectrum.

**2-(Hydroxyphenylmethyl)-2-methylcyclohexanone (31).** A solution of 2-methyl-1-(trimethylsiloxy)cyclohexene (**30**; 233 mg, 1.26 mmol) and benzaldehyde (122 mg, 1.15 mmol) in 1 mL of THF was added to a suspension of TBAF (15 mg, 0.06 mmol) in 0.5 mL of THF at −78 °C. After 5 min, the bath temperature was raised to −30 °C, and the reaction mixture was stirred for 2 h at this temperature, quenched with 10 mL of $AcOH/H_2O$, and stirred overnight at room temperature. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 3 mL). The crude product (210 mg) obtained after drying and concentration of the extract was purified by preparative TLC (hexane/ether) and separated into a diastereomeric mixture of the title aldol (156 mg, 62%). Examination of the benzylic proton signal in the NMR spectrum indicated the threo–erythro ratio to be 7:3.[33] This mixture exhibited spectra completely identical with the reported data[5a] except for the assignment of the diastereomers:[33] IR (neat) 3460 (br, OH), 1695 (vs, C=O); $^1$H NMR ($CCl_4$) 0.90 (s, 0.9 H, $CH_3$, threo), 1.00 (s, 2.1 H, $CH_3$, erythro), 0.85–2.90 (m, 8 H, $CH_2$, $CH_2C$=O), 3.58 (br s, 1 H, OH), 4.85 (s, 0.7 H, CHOH threo), 4.93 (s, 0.3 H, CHOH erythro), 7.23 (s, 5 H, $C_6H_5$).

**2-(Hydroxyphenylmethyl)-6-methylcyclohexanone (33).** A solution of 3-methyl-2-(trimethylsiloxy)cyclohexene (**32**; 213 mg, 1.15 mmol) and benzaldehyde (185 mg, 1.15 mmol) in 1 mL of THF was added to a suspension of TBAF (15 mg, 0.06 mmol) in 0.5 mL of THF kept at −20 °C. After being stirred for 2 h at −20 °C, the reaction mixture was quenched with 1 mL of $AcOH/H_2O$ (1:2) and stirred overnight at room temperature. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 3 mL). An oil obtained after drying and concentration of the extract was purified by preparative TLC to afford a diastereomeric mixture of the title compound (170 mg, 68%). The product obtained by this experiment and another duplicate experiment (427 mg) was separated by column chromatography (25 g of silica gel, hexane/ether), separating into four successive fractions: A–D.

A was the trans erythro isomer: 50 mg; IR (neat) 3520 (br, OH), 1710 (C=O); $^1$H NMR ($CCl_4$) 1.01 (d, 3 H, $J$ = 5.0 Hz, $CH_3$), 0.75–2.8 (m, 8 H, $CH_2CHC$=O), 3.00 (br, s, 1 H, OH), 5.25 (d, 1 H, $J$ = 2 Hz, CHOH), 7.23 (s, 5 H, $C_6H_5$).

B was a mixture of the cis threo and erythro isomers: 89 mg (threo/erythro ratio of 3:5); IR (neat) 3440 (br, OH), 1700 (vs, C=O); $^1$H NMR ($CCl_4$) 0.96 (d, 1.1 H, $J$ = 6 Hz, $CH_3$, threo), 1.03 (d, 1.9 H, $J$ = 7 Hz, $CH_3$, erythro), 0.7–2.8 (m, 8 H, $CH_2$, CHO=O), 2.92 and 3.41 (2 br s, 1 H, OH, threo and erythro), 4.66 (d, 0.37 H, $J$ = 8 Hz, CHOH threo), 5.15 (d, 0.63 H, $J$ = 3 Hz, CHOH, erythro), 7.20 (s, 5 H, $C_6H_5$).

C was the cis erythro isomer (45 mg) obtained as a semisolid: IR (KBr) 3410 (s, OH), 1710 (vs, C=O); $^1$H NMR ($CCl_4$) 1.03 (d, 3 H, $J$ = 7 Hz, $CH_3$) 0.7–2.8 (m, 8 H, $CH_2$, CHC=O), 2.92 (br s, 1 H, OH), 5.18 (d, 1 H, $J$ = 3 Hz, CHOH), 7.20 (s, 5 H, $C_6H_5$).

The last fraction D was the trans threo isomer (140 mg), obtained as a solid material: IR (KBr) 3400 (s, OH), 1705 (vs, C=O); $^1$H NMR ($CCl_4$) 1.10 (d, 3 H, $J$ = 7 Hz, $CH_3$), 0.6–0.3 (m, 8 H, $CH_2$, CHC=O), 3.50 (br s, 1 H, OH), 4.77 (d, 1 H, $J$ = 8 Hz, CHOH), 7.20 (s, 5 H, $C_6H_5$).

Thus, the threo–erythro ratio was 54:46, and the axial–equatorial ratio was 59:41. The spectra of these four compounds were identical with the reported data.[5a]

**Reaction of 4-*tert*-Butyl-1-methyl-2-(trimethylsiloxy)-cyclohexene (34) and Benzaldehyde.** A THF solution (2 mL) of the enol silyl ether **34** (184 mg, 0.77 mmol) and benzaldehyde (110 mg, 1.1 mmol) was mixed with 1 mL of THF containing TBAF (18 mg, 0.07 mmol) at −45 °C. The resulting solution was maintained at −35 °C for 1.5 h and poured into hexane. The mixture was washed with water, dried, and concentrated to leave the crude aldol trimethylsilyl ethers as an oil (265 mg). TLC purification with 1:10 ether/hexane mixture as the eluent gave a mixture of the axial aldol silyl ether **35a**: $R_f$ 0.35; 181 mg (68% yield; threo/erythro ratio of 6:4). This diastereomeric mixture (86 mg, 0.25 mmol) was dissolved in a mixture of methanol (5 mL) and 0.1 N HCl (0.4 mL), and the solution was kept at room temperature for 1 h. The mixture was then diluted with water and extracted with ether. The combined extract was dried and concentration to leave an oil (68 mg). TLC separation of this residue (1:2 ether/hexane) afforded the axial, erythro aldol ($R_f$ 0.38; 14 mg, 21%) and the axial, threo isomer ($R_f$ 0.23; 40 mg, 59%) as colorless prisms. Both compounds were identical in all respects with the authentic samples.[9a]

The axial, threo isomer: mp 120.5–122 °C (hexane); IR ($CCl_4$) 3620 (s, OH), 3440 (s, OH) 1705 (vs, C=O); $^1$H NMR ($CCl_4$) 0.76 (s, 3 H, $CH_3$), 0.94 (s, 9 H, $t$-$C_4H_9$), 1.1–2.0 (m, 5 H, $CH_2$, CH), 2.2–2.6 (m, 2 H, $CH_2C$=O), 2.66 (d, 1 H, $J$ = 3 Hz, OH), 5.08 (d, 1 H, $J$ = 3 Hz, CHOH), 7.24 (s, 5 H, $C_6H_5$); mass spectrum, $m/e$ 225, 221, 207, 192, 168, 124, 121, 119, 117, 112, 111, 106, 105, 97, 83, 77.

The axial erythro isomer: mp 98.5–100 °C (hexane); IR ($CCl_4$) 3630 (s, OH), 3480 (s, OH), 1703 (vs, C=O); $^1$H NMR ($CCl_4$) 0.85 (s, 3 H, $CH_3$), 0.90 (s, 9 H, $t$-$C_4H_9$), 1.0–1.8 (m, 4 H, $CH_2$), 2.1–2.5 (m, 4 H, $CH_2C$=O, OH, CH), 4.81 (d, 1 H, $J$ = 4 Hz, CHOH), 7.20 (s, 5 H, $C_6H_5$); mass spectrum, $m/e$ 207, 192, 168, 112, 111, 106, 105.

The NMR spectrum of the crude silyl ether product was compared carefully with those of four possible diastereomers,[9a] revealing that only axial adducts were formed. Authentic samples of the four isomers were prepared as follows. To a pyridine (0.2 mL) solution of the axial, threo aldol (7.4 mg, 0.027 mmol) were added hexamethyldisilazane (0.13 mL) and trimethylchlorosilane (0.1 mL). The resulting mixture was allowed to stand at room temperature for 1 h, diluted with hexane, and treated with water. The dried organic layer was evaporated to give the corresponding trimethylsilyl ether (8 mg, 85%) as colorless crystals: mp 53–54 °C; IR ($CCl_4$) 1712 (vs, C=O), 1247 (s, CO), 1064 (s, CO), 888 (CSi), 872 (s, CSi), 834 (CSi); $^1$H NMR ($CCl_4$) 0.04 (s, 9 H, $SiCH_3$), 0.86 (s, 3 H, $CH_3$), 0.97 (s, 9 H, $t$-$C_4H_9$), 1.2–2.0 (m, 5 H, $CH_2$, CH), 2.32 (m, 2 H, $CH_2C$=O), 5.10 (s, 1 H, CHOSi), 7.27 (s, 5 H, $C_6H_5$); mass spectrum, $m/e$ 364 ($M^+$), 331 ($M^+$ − 15), 240 ($M^+$ − 106), 179 ($M^+$ − 167). Other isomers were prepared in a similar manner. The axial, erythro isomer: IR ($CCl_4$) 1709 (vs, C=O), 834 (s, CSi); $^1$H NMR ($CCl_4$) −0.08 (s, 9 H, $SiCH_3$), 0.76 (s, 3 H, $CH_3$), 0.92 (s, 9 H, $t$-$C_4H_9$), 1.2–1.9 (m, 5 H, $CH_2$, CH), 2.32 (m, 2 H, $CH_2C$=O), 4.80 (s, 1 H, CHOSi), 7.20 (s, 5 H, $C_6H_5$); mass spectrum, 331 ($M^+$ − 15), 240 ($M^+$ − 106), 179 ($M^+$ − 167). The equatorial, threo isomer: IR ($CCl_4$) 1699 (vs, C=O), 843 (s, CSi); $^1$H NMR ($CCl_4$) −0.14 (s, 9 H, $SiCH_3$), 0.82 (s, 9 H, $t$-$C_4H_9$), 0.9–2.4 (m, 8 H, $CH_2$, CH) 1.20 (s, 3 H, $CH_3$), 5.03 (s, 1 H, CHOSi), 7.20 (m, 5 H, $C_6H_5$); mass spectrum, $m/e$ 364 ($M^+$), 331 ($M^+$ − 15), 240 ($M^+$ − 106), 179 ($M^+$ − 167). The equatorial, erythro isomer: IR ($CCl_4$) 1700 (vs, C=O), 840 (s, CSi); $^1$H NMR ($CCl_4$) 0.15 (s, 9 H, $SiCH_3$), 0.84 (s, 3 H, $CH_3$), 0.96 (s, 9 H, $t$-$C_4H_9$), 1.1–2.6 (m, 8 H, $CH_2$, CH), 5.14 (s, 1 H, CHOSi), 7.26 (m, 5 H, $C_6H_5$); mass spectrum, $m/e$ 346 ($M^+$), 331 ($M^+$ − 15), 240 ($M^+$ − 106), 179 ($M^+$ − 167).

**Reaction of Cyclohexanone and Benzaldehyde in the Presence of TBAF.** A solution of cyclohexanone (196 mg, 2.0 mmol), benzaldehyde (212 mg, 2.0 mmol), and tetralin (an internal standard, 150 mg) in 3 mL of THF was added at room temperature to TBAF (53 mg, 0.2 mmol). From the homogeneous reaction mixture which was stirred at room temperature were taken aliquots (0.5 mL) after 40 min and 41 h. Each was diluted with hexane and analyzed by GLC (5% XE-60 on Chromosorb P(AW), 3 mm × 1 m, 70 °C). The starting materials were not at all consumed even after 41 h. Typical retention times were 2.65, 4.40, and 5.28 min for cyclohexanone, benzaldehyde, and tetralin, respectively.

**Reaction of 1-(Trimethylsiloxy)cyclododecene and Benzophenone in the Presence of TBAF.** A solution of the silyl ether (440 mg, 1.30 mmol) and benzophenone (237 mg, 1.30 mmol) in 1 mL of THF was added to a suspension of TBAF (17 mg, 0.07 mmol) in 0.5 mL of THF at −78 °C. After being stirred for 4 h at −78 °C, the reaction mixture was diluted with 30 mL of hexane

at −78 °C, filtered, and concentrated in vacuo to leave 656 mg of a yellow oil, and the mixture was analyzed by NMR. Comparison of the relative intensities of signals at δ 4.52 (t, CH=) and 5.92 (s) indicated 87% recovery of the enol silyl ether. Chromatography on silica gel afforded 205 mg of benzophenone (86% recovery).

**Preparation of 2-(1-Butyl-1-hydroxypentyl)cyclohexanone.** To a stirred solution of $TiCl_4$[5] (2.21 g, 12 mmol) and 5-nonanone (1.67 g, 11 mmol) in 20 mL of methylene chloride was added a solution of 1-(trimethylsiloxy)cyclohexene (1.98 g, 12 mmol) in 60 mL of methylene chloride at 0 °C. After 5 min at 0 °C and then 4 h at room temperature the mixture was quenched with water (50 mL) and extracted with methylene chloride (3 × 20 mL). The combined extracts were washed with aqueous NaCl, dried, and concentrated in vacuo to give an oil (3.75 g). The oil was purified by column chromatography (100 g of silica gel, hexane/ether) to afford the title aldol: 1.96 g (70%); $R_f$ 0.32 (benzene). Further purification on preparative TLC gave an analytical sample. The aldol underwent a retroaldol reaction[40] on GLC at a temperature above 80 °C and could not be analyzed this way: IR (neat) 3480 (s, OH), 1690 (vs, C=O); $^1$H NMR ($CCl_4$) 0.8–2.7 (m, 27 H), 3.50 (s, OH). Anal. ($C_{15}H_{28}O_2$) C, H.

**Preparation of 2-[1-Butyl-1-(trimethylsiloxy)pentyl]-cyclohexanone (37).** A mixture of *N*-(trimethylsilyl)imidazole (0.5 mL) and trimethylchlorosilane (0.5 mL) was added to a solution of 2-(1-butyl-1-hydroxypentyl)cyclohexanone (176 mg, 0.69 mmol) in 2 mL of THF at room temperature. After being stirred overnight, the reaction mixture was diluted with 20 mL of hexane, filtered, and concentrated in vacuo to give the title silyl ether (237 mg, 95%), which was pure by chromatographic ($R_f$ 0.66, benzene) and spectroscopic analysis: IR (neat) 1710 (vs, C=O); $^1$H NMR ($CCl_4$) 0.10 (s, 9 H, $CH_3Si$), 0.6–2.6 (m, 27 H, $CH_3$, $CH_2$, CHO=O).

**Decomposition of 37 in the Presence of TBAF.** A solution of **37** (164 mg, 0.50 mmol) and tetralin (an internal standard) in 1 mL of THF was added to a suspension of TBAF (18 mg, 0.07 mmol) in 0.5 mL of THF at room temperature. After being stirred for 1 h, followed by an aqueous workup, the reaction mixture was analyzed by TLC and quantitative GLC analysis (10% QF-1 on Diasolid L, 3 mm × 2 m, 70 °C). The former indicated the complete absence of the starting silyl ether or its parent aldol, and the latter showed that cyclohexanone (81%) and 5-nonanone (90%) were regenerated.

**Reaction of 3-(Trimethylsiloxy)-2-pentene (19) and Benzaldehyde in the Presence of Phenyloxirane.** A mixture of **19** (217 mg, 1.37 mmol) and phenyloxirane (150 mg, 1.25 mmol) in 2.5 mL of THF was treated with TBAF (16 mg, 0.063 mmol) at −78 °C for 5 h. The reaction mixture was diluted with 30 mL of hexane at −78 °C, filtered, and concentrated in vacuo to leave 440 mg of a yellow oil. TLC analysis showed the presence of a small amount of **19** which was used in excess ($R_f$ 0.75, benzene) as well as phenyloxirane ($R_f$ 0.5) and the aldol adduct ($R_f$ 0.4). 1,1,2,2-Tetrachloroethane (105 mg, 0.625 mmol) was added to the crude mixture, and this was analyzed by $^1$H NMR ($CCl_4$). The spectrum agreed with a mixture of 4-methyl-5-phenyl-5-(trimethylsiloxy)-3-pentanone (**20**, 93% yield) and phenyloxirane (100% recovery). Yields were based on the intensities of signals at δ 7.13 ($C_6H_5$), around 4.7 (benzylic protons of the adduct), and centered at 3.70 (m, benzylic protons of phenyloxirane).

**Reaction of 3-(Trimethylsiloxy)-2-pentene (19) and Diethyl Ethylidenemalonate in the Presence of 4-Phenyl-2-butanone.** A mixture of 3-(trimethylsiloxy)-2-pentene (95 mg, 0.60 mmol), 4-phenyl-2-butanone (89 mg, 0.60 mmol), and diethyl ethylidenemalonate (102 mg, 0.55 mmol) in 2 mL of THF was added dropwise to TBAF (158 mg, 0.605 mmol) kept at −20 °C. The reaction mixture was stirred for 40 min at that temperature and poured into water. After extraction with ether (3 × 10 mL), the combined extract was washed with water, dried, and concentrated. The remaining oil was subjected to silica gel column chromatography (30 g, hexane/ether). Thus, 72 mg of benzylacetone (80% recovery excluding the excess), 28 mg of diethyl ethylidenemalonate (ca. 27%, slightly impure by NMR), and the adduct ethyl 2-(ethoxycarbonyl)-3,4-dimethyl-5-oxoheptanoate (**38**; 100 mg, 74%) were separated. None of the ketone or the malonate was isolated. The adduct, purified by bulb-to-bulb distillation [bp 95 °C (bath temperature, 0.06 mm)], exhibited the following spectra, which indicated that the product was 1:1 mixture of diastereomers: IR (neat) 1730 (br, C=O); $^1$H NMR ($CCl_4$) 0.75–1.15 (m, 9 H, $CH_3$), 1.28 (t, 6 H, $J$ = 7 Hz, $CH_3CH_2O$), 2.25–2.9 (m, 4 H, $CH_2C$=O, CHO=O, CH), 3.20 (d, 0.5 H, $J$ = 8 Hz), 3.40 (d, 0.5 H, $J$ = 6 Hz, CHC=O), 4.15 (q, 4 H, $J$ = 7 Hz, $CH_2O$); mass spectrum, $m/e$ (relative intensity) 272 ($M^+$, 1.5), 196 (20), 159 (39), 141 (54), 113 (37), 57 (100), 29 (88).

**3,5-Diphenyl-1-(trimethylsiloxy)-2,4-dioxabicyclo[4.4.0]-decane (39).** To a THF solution (10 mg) of **5** (680 mg, 4.0 mmol) and benzaldehyde (850 mg, 8.0 mmol) was added TBAF (26 mg, 0.1 mmol) in 0.2 mL of THF at −78 °C. The solution was maintained at −78 °C for 3 h and then at −30 °C for 12 h, diluted with 80 mL of hexane, and quenched by addition of water. The organic layer was dried and evaporated. NMR analysis of the residue indicated the presence of threo aldol trimethylsilyl ether, erythro aldol trimethylsilyl ether, and the title 1:2 adduct (**39**) in 50%, 13%, and 37% yields, respectively. TLC separation (40:1 hexane/ether, two developments) afforded the 1:2 adduct ($R_f$ 0.27, 373 mg, 24%) as colorless needles. Recrystallization from hexane gave an analytical sample: mp 119–120.5 °C; IR ($CCl_4$) 843 (CSi); NMR ($CCl_4$) 0.24 (s, 9 H, $SiCH_3$), 0.9–1.8 (m, 8 H, $CH_2$), 2.14 (m, 1 H, C(6) H), 5.51 (br s, 1 H, C(5) H), 6.05 (s, 1 H, C(3) H), 7.1–7.6 (m, 10 H, $C_6H_5$); mass spectrum, $m/e$ 382 ($M^+$), 292 ($M^+$ − 90), 276 ($M^+$ − 106), 186 ($M^+$ − 196). Anal. ($C_{23}H_{30}O_3Si$) C, H.

The crystalline 1:2 adduct (18 mg) was dissolved in 4 mL of 1:1 hexane/ether and mixed with 0.4 mL of 1:10 1 N HCl/$CH_3OH$. The mixture was stirred at room temperature for 4 h and diluted with water. The organic layer was dried and concentrated. The NMR analysis indicated that the residue (16 mg) consisted of the erythro aldol, benzaldehyde, and benzaldehyde dimethyl acetal in a 1:0.2:0.5 ratio.

**Reaction of 3-(Trimethylsiloxy)-2-pentene (19) and 2,2-Dimethyl-3-phenylpropanal in the Presence of TBAF.** A solution of **19** (158 mg, 1.0 mmol) and 2,2-dimethyl-3-phenylpropanal (162 mg, 1.0 mmol) in 1 mL of THF was added to a suspension of TBAF (13 mg, 0.05 mmol) at −78 °C. After being stirred for 3 h at −78 °C, the reaction mixture was diluted with 20 mL of hexane, filtered, and concentrated in vacuo to give an oil (295 mg). The oil was purified on preparative TLC (hexane/ether) to afford two materials: A followed by B.

The structure of A was established as a 1:2 adduct (**41**) as follows. The molecular weight of A was determined to be approximately 460 by the Rast method.[41] The observed molecular weight of A was close to that of 1:2 adduct. Further, A (49 mg, 0.10 mmol, as a 1:2 adduct) was hydrolyzed with $CH_3OH$/HCl (1.2 N, 0.5 mL) to give a diastereomeric mixture of the aldol **40b** (20 mg, 0.079 mmol) and 2,2-dimethyl-3-phenylpropanal (11 mg, 0.067 mmol). The threo/erythro ratio of **40b** was 11:9. These facts as well as the IR and the NMR spectra indicated that A was 6-ethyl-5-methyl-2,4-bis(1,1-dimethyl-2-phenylethyl)-6-(trimethylsiloxy)-1,3-dioxacyclohexane (**41**), 129 mg (26%). It showed no detectable parent peak in its mass spectrum. The following spectral data were obtained for A: bp 196–199 °C (bath temperature; 0.06 mm); IR (neat) 2950, 840; $^1$H NMR ($CCl_4$) 0.07 (s, 9 H, $CH_3Si$), 0.7–1.9 (m, 27 H, including 2 s at 0.93 and 1.04, $CH_3$, $CH_2$, CH), 2.70 (s, 4 H, $CH_2C_6H_5$), 3.90 (d, $J$ = 2 Hz, 1 H, CHO), 4.67 (s, 1 H, OCHO), 7.13 (s, 10 H, $C_6H_5$).

The threo aldol adduct showed the following spectra: IR (neat) 3450 (s, OH), 1705 (vs, C=O); $^1$H NMR ($CCl_4$) 0.80 (s, 3 H, $CH_3$), 0.90 (s, 3 H, $CH_3$), 1.03 (t, $J$ = 8 Hz, 3 H, $CH_2CH_3$), 1.17 (d, $J$ = 8 Hz, 3 H, $CHCH_3$), 2.2–2.9 (m, 5 H, CHC=O, $CH_2C_6H_5$), 3.57 (d, $J$ = 3 Hz, 1 H, CHOH), 3.90 (br s, 1 H, OH), 7.17 (s, 5 H, $C_6H_5$). Anal. ($C_{16}H_{24}O_2$) C, H.

The erythro isomer showed the following spectral data: IR (neat) 3475 (s, OH), 1695 (vs, C=O); $^1$H NMR ($CCl_4$) 0.73 (s, 3 H, $CH_3$), 0.85 (s, 3 H, $CH_3$), 1.05 (t, $J$ = 6 Hz, 3 H, $CH_2CH_3$), 1.13 (d, $J$ = 7 Hz, 3 H, $CHCH_3$), 2.25–3.10 (m, 6 H, $CH_2C$=O, CHC=O, $C_6H_5CH$, OH), 3.50 (d, $J$ = 2 H, 1 H, CHOH), 7.10 (s, 5 H, $C_6H_5$). Anal. ($C_{16}H_{24}O_2$) C, H.

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B was submitted to bulb-to-bulb distillation and separated into two materials: A (54 mg, 11%) and C, which was assigned in the following manner to 7-phenyl-4,6,6-trimethyl-5-(trimethylsiloxy)-3-heptanone (**40a**): 46 mg (11%); bp 110–120 °C (bath temperature; 0.25 mm); IR (neat) 1710 (vs, C=O); $^1$H NMR ($CCl_4$) 0.11 (s, 9 H, $CH_3Si$), 0.75–1.25 (m, including br s at 0.75 and d at 1.07, $J$ = 8 Hz, 12 H, $CH_2$, $CH_3$), 2.23–2.73 (m, including s at 2.53, $C_6H_5CH_2$, $CH_2C$=C, CHC=O), 3.63 (d, $J$ = 4 Hz, 1 H, CHO), 7.20 (s, 5 H, $C_6H_5$).

C gave the threo aldol adduct on hydrolysis, which supports the above assignment. Thus, the material balance of 85% of the starting aldehyde was accounted for.

**Time Dependency of the Product Distribution of the Reaction of 1-(Trimethylsiloxy)cyclohexene and Benzaldehyde.** In seven glass tubes was placed 0.3 mL of a THF solution containing TBAF (25 mg, 0.10 mmol). To each solution cooled at −78 °C was added a mixture of **5** (160 mg, 0.94 mmol) and benzaldehyde (123 mg, 1.16 mmol) in 2 mL of THF, and the resulting mixture was kept at −78 °C. After an appropriate period, the reaction mixture was diluted with 10 mL of hexane at ambient temperature. The mixture was treated with water, and the hexane layer was dried and evaporated to give the aldol trimethylsilyl ethers as a crude oil. The residue was dissolved in 3 mL of 1:9 1 N HCl/$CH_3OH$ and allowed to stand at room temperature for 5 min. The solution was diluted with 1:1 hexane/ether and shaken with water. The organic solution was dried and concentrated to give the crude aldol product, which was analyzed by NMR ($CCl_4$) with added 1,1,2,2-tetrachloroethane (79 mg, 0.47 mmol). The threo to erythro ratio was determined on the basis of relative intensities of signals due to the CH(OH)$C_6H_5$ protons (threo $\delta$ 4.66, erythro $\delta$ 5.30) and tetrachloroethane ($\delta$ 5.93). The result is shown in Figure 1.

**Time Dependency of the Product Distribution in the Reaction of 2-Methyl-1-(trimethylsiloxy)cyclohexene (30) and Benzaldehyde.** The procedure described above was followed in the reaction of **30** (92 mg, 0.50 mmol) and benzaldehyde (64 mg, 0.60 mmol) in the presence of TBAF (14 mg, 0.05 mmol). Yield of the aldol **31** and the diastereomeric ratio were determined by examining the relative intensities of the CH(OH)$C_6H_5$ signal (threo $\delta$ 4.87 and erythro $\delta$ 4.99)[33] and the standard tetrachloroethane. The result is summarized in Figure 2.

**One-Pot Preparation of 5-(Trimethylsiloxy)-2-methyl-5-phenyl-3-pentanone.** A solution of methyl isopropyl ketone (395 mg, 4.60 mmol) and ethyl (trimethylsilyl)acetate[35a] (809 mg, 5.06 mmol) in 1 mL of THF was added to a suspension of TBAF (12 mg, 0.05 mmol) in 0.5 mL of THF at 0 °C. After the mixture was stirred for 2 h at 0 °C, the cooling bath temperature was lowered to −78 °C. A solution of benzaldehyde (536 mg, 5.06 mmol) in 1 mL of THF and another portion of TBAF (50 mg, 0.19 mmol) in 1 mL of THF were added to the reaction mixture, which was subsequently stirred for 2 h at −20 °C. The reaction mixture was diluted with 30 mL of hexane and filtered. After concentration in vacuo, the crude product (881 mg) was purified by preparative TLC (hexane/ether) to yield two products: A followed by B.

A was the title compound: 631 mg (52%); bp 90–95 °C (bath temperature; 0.06 mm); IR (neat) 1715 (vs, C=O); $^1$H NMR ($CCl_4$) 0.30 (s, 9 H, $CH_3Si$), 1.07 (s, 3 H, $J$ = 8 Hz, $CH_3CH$), 1.13 (d, 3 H, $J$ = 8 H, $CH_3CH$), 2.35–3.3 (m, 3 H, CHC=O, $CH_2C$=O), 5.30 (dd, 1 H, $J$ = 4, 6 Hz, CHO), 7.30 (s, 5 H, $C_6H_5$); mass spectrum, $m/e$ (relative intensity) 264 ($M^+$, 4), 249 (9), 221 (28), 179 (63), 140 (25), 130 (11), 75 (59), 73 (100).

B was spectroscopically identified as 2-methyl-5-phenyl-4-penten-3-one: 128 mg (16%); IR (neat) 1695 (s, C=O), 1610 (vs, C=C); $^1$H NMR ($CCl_4$) 1.13 (d, 6 H, $J$ = 6 Hz, $CH_3$), 2.91 (m, 1 H, CHC=O), 6.73 (d, 1 H, $J$ = 16 Hz, C=CHC=O), 7.25–7.75 (m, 6 H, olefinic and aromatic protons).

**Spectral Properties. 2-[1-(Trimethylsiloxy)-3-phenyl-(*E*)-2-propenyl]cyclohexanone (12)**: mp 45.5–48.5 °C (prisms, hexane); IR ($CCl_4$) 1703 (vs, C=O), 965 (s, *trans*-C=C), 840 (vs, CSi); $^1$H NMR ($CCl_4$) 0.11 (s, 9 H, $SiCH_3$), 1.5–2.6 (m, 9 H, $CH_2$, CH), 4.78 (m, 1 H, CHO), 6.12 (dt, 1 H, $J$ = 15, 5 Hz, CH=$CHC_6H_5$), 6.51 (dd, 1 H, $J$ = 15 and 3 Hz, CH=$CHC_6H_5$), 7.1–7.3 (m, 5 H, $C_6H_5$); mass spectrum, 302 ($M^+$), 237 ($M^+$ − 15), 205 ($M^+$ − 97), 170 ($M^+$ − 132).

**2-(1-Hydroxy-3-phenylpropyl)cyclohexanone (13)**: bp 145–148 °C (bath temperature; 0.26 mm); IR (neat) 3405 (br, OH), 1700 (vs, C=O); $^1$H NMR ($CCl_4$) 0.75–3.3 (m, 13 H, $CH_2$), 3.35 (br s, 1 H, OH), 3.8–4.3 (m, 1 H, CHOH), 7.18 (s, 5 H, $C_6H_5$). Anal. ($C_{15}H_{20}O_2$) C, H. This compound was identical with the authentic sample.[9c]

**2-(Benzoylhydroxyphenylmethyl)cyclohexanone (14)**: mp 131–133 °C (hexane/ethyl acetate); IR ($CCl_4$) 3527 (s, OH), 1696 and 1677 (vs, C=O); $^1$H NMR ($CCl_4$) 1.2–2.7 (m, 9 H, $CH_2$, CH), 4.21 (s, 1 H, OH), 7.0–7.9 (m, 10 H, $C_6H_5$); mass spectrum, $m/e$ 308 ($M^+$), 291 ($M^+$ − 17), 203 ($M^+$ − 105), 105 ($M^+$ − 203). The structure was identified by comparison with the authentic sample.[42]

**2-[(2-Furyl)hydroxymethyl]cycloheptanone (15)**, the threo isomer: $R_f$ 0.20 (ether/hexane, 1:1); IR ($CCl_4$) 3477 (s, OH), 1689 (vs, C=O); $^1$H NMR ($CCl_4$) 1.0–2.1 (m, 8 H, $CH_2$), 2.57 (m, 2 H, $CH_2C$=O), 3.25 (m, 2 H, CHCO, OH; 1 H signal on $D_2O$ treatment), 4.48 (d, 1 H, 8 Hz, CHOH), 6.30 (m, 2 H, protons of furyl group), 7.38 (m, 1 H, furyl proton); mass spectrum, $m/e$ 208 ($M^+$), 190, 165, 112.

The erythro isomer: $R_f$ 0.33 (ether/hexane 1:1) IR ($CCl_4$) 3545 (s, OH), 1687 (vs, C=O); $^1$H NMR ($CCl_4$) 1.0–2.1 (m, 8 H, $CH_2$), 2.54 (m, 2 H, $CH_2CO$), 2.8–3.5 (m, 2 H, CHCO and OH; 1 H m at 3.00 upon $D_2O$ treatment), 5.09 (d, 1 H, $J$ = 3.8 Hz, CHO), 6.30 (m, 2 H, furyl protons), 7.34 (1 H, furyl proton); mass spectrum $m/e$ 208 ($M^+$), 190, 112. Anal. ($C_{12}H_6O_3$) C, H.

**2-(Hydroxyphenylmethyl)cycloheptanone (16)**, the erythro isomer: $R_f$ 0.34 (hexane/ethyl acetate, 3:1); mp 79–80.5 °C; IR ($CCl_4$) 3527 (s, OH), 1685 (vs, C=O); $^1$H NMR ($CCl_4$) 1.1–2.1 (m, 8 H, $CH_2$), 2.48 (m, 2 H, $CH_2CO$), 2.70 (m, 1 H, CHCO), 3.15 (br s, 1 H, OH, disappeared on $D_2O$ treatment), 4.09 (br s, 1 H, CHOH, d, $J$ = 3 Hz on $D_2O$ treatment), 7.24 (s, 5 H, $C_6H_5$); mass spectrum, $m/e$ 218 ($M^+$), 200, 175, 112. Anal. ($C_{14}H_{18}O_2$) C, H.

The threo isomer: $R_f$ 0.27; IR ($CCl_4$) 3495 (s), 1690 (vs, C=O); $^1$H NMR ($CCl_4$) 1.1–2.0 (m, 8 H, $CH_2$), 2.42 (m, 2 H, $CH_2CO$) 2.83 (m, 1 H, CHCO), 3.18 (br s, 1 H, OH, disappeared on $D_2O$ treatment), 4.70 (br d, 1 H, $J$ = 8 Hz, CHOH), 7.24 (s, 5 H, $C_6H_5$); mass spectrum, $m/e$ 218 ($M^+$), 200, 175, 112.

**2-Methyl-1-phenyl-1-(trimethylsiloxy)-3-pentanone (20)**: bp 80–110 °C (bath temperature; 0.03 mm); IR (neat) 1710 (vs, C=O); $^1$H NMR ($CCl_4$) 0.08 (s, 9 H, $CH_3Si$), 0.83 (t, $J$ = 7 Hz, 3 H, $CH_3CH_2$), 1.20 (d, $J$ = 6 Hz, 3 H, $CH_3CH$), 1.7–3.0 (m, 3 H, $CH_2C$=O, CHC=O), 4.45–4.85 (m, 1 H, CHO), 7.18 (s, 5 H, $C_6H_5$); mass spectrum, $m/e$ (relative intensity) 249 ($M^+$ − 15, 6), 179 (100), 75 (44), 73 (89); high-resolution mass spectrum, $m/e$ 249.1308 (calcd for $C_{14}H_{21}O_2Si$, 249.1309).

**5-Hydroxy-4-methyl-6-decen-3-one (21)**: bp 80–85 °C (bath temperature; 0.03 mm); IR (neat) 3425 (br, OH), 1710 (vs, C=O); $^1$H NMR ($CCl_4$) 0.7–2.7 (m, 16 H, $CH_3CH_2$, $CH_3CH$, CHC=O, CHC=O), 2.77 (s, 1 H, OH; disappeared on $D_2O$ treatment), 4.05–4.35 (m, 1 H, CHO), 5.35–5.65 (m, 2 H, CH=); mass spectrum, $m/e$ (relative intensity) 166 ($M^+$ − 18, 7), 123 (22), 86 (67), 83 (60), 69 (65), 56 (63), 29 (100); high-resolution mass spectrum, $m/e$ 166.1329 (calcd for $C_{11}H_{18}O_2$, 166.1356).

**3-(Hydroxyphenylmethyl)-2,6-dimethylheptan-4-one (23)**, the threo isomer: $R_f$ 0.24 (hexane/ethyl acetate 10:1); IR ($CCl_4$) 3622 (s, OH), 3485 (s, OH), 1705 (vs, C=O); $^1$H NMR ($CCl_4$) 0.58 (d, 3 H, $J$ = 6 Hz, $CH_3$), 0.73 (d, 3 H, $J$ = 6 Hz, $CH_3$), 0.96 (d, 3 H, $J$ = 5 Hz, $CH_3$), 1.03 (d, 3 H, $J$ = 5 Hz, $CH_3$), 1.5–2.4 (m, 5 H, CH, $CH_3CO$, OH; 4 H m on $D_2O$ treatment), 2.74 (dd, 1 H, $J$ = 4, 8 Hz, CHCO), 4.83 (d, 1 H, $J$ = 8 Hz, CHO), 7.22 (s, 5 H, $C_6H_5$); mass spectrum, $m/e$ 248 ($M^+$), 230 ($M^+$ − 18), 205 ($M^+$ − 43), 142 ($M^+$ − 106). Anal. ($C_{16}H_{24}O_2$) C, H.

The erythro isomer: $R_f$ 0.32; IR ($CCl_4$) 3625 (w, OH), 3485 (s, OH), 1690 (vs, C=O); $^1$H NMR ($CCl_4$) 0.59 (d, 3 H, $J$ = 6 Hz, $CH_3$), 0.74 (d, 3 H, $J$ = 7 Hz, $CH_3$), 1.4–2.3 (m, 4 H, CH and $CH_2CO$), 2.51 (dd, 1 H, $J$ = 4, 8 Hz, CHCO), 3.43 (d, 1 H, $J$ = 8 Hz, OH), 4.85 (dd, 1 H, $J$ = 8 Hz, CHOH), 7.20 (s, 5 H, $C_6H_5$); mass spectrum, $m/e$ 248 ($M^+$), 230, 205, 142. Anal. ($C_{16}H_{24}O_2$) C, H.

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**Registry No.** **5**, 6651-36-1; **6a**, 62572-35-4; *erythro*-**6b**, 13161-18-7; *threo*-**6b**, 42052-56-2; **7**, 5682-83-7; **8**, 22081-48-7; *threo*-**10**, 71444-30-9; *erythro*-**10**, 71444-29-6; *threo*-**11**, 84624-42-0; *erythro*-**11**, 84624-41-9; **12**, 84896-21-9; **13**, 60669-65-0; **14**, 84896-22-0; *threo*-**15**, 84896-23-1; *erythro*-**15**, 84896-24-2; *threo*-**16**, 81640-06-4; *erythro*-**16**, 81640-05-3; **17**, 19980-43-9; **18**, 26620-52-0; **19**, 17510-47-3; **20**, 84896-25-3; **21**, 84896-26-4; **22**, 2346-34-1; *threo*-**23**, 84896-27-5; *erythro*-**23**, 84896-28-6; **24**, 17510-46-2; **25a**, 84896-29-7; **25b**, 42052-52-8; **26**, 13735-81-4; **27**, 84896-30-0; **28**, 17082-61-0; *threo*-**29**, 84896-31-1; *erythro*-**29**, 84896-32-2; **30**, 19980-35-9; *threo*-**31**, 54322-99-5; *erythro*-**31**, 54322-98-4; **32**, 19980-33-7; **33** (isomer 1), 54323-00-1; **33** (isomer 2), 54353-03-6; **33** (isomer 3), 54323-00-1; **33** (isomer 4), 54353-01-4; **34**, 62572-34-3; **35a** (isomer 1), 62623-74-9; **35a** (isomer 2), 62572-37-6; **35a** (isomer 3), 84680-50-2; **35a** (isomer 4), 84680-51-3; **37**, 84896-34-4; *threo*-**38**, 84896-35-5; *erythro*-**38**, 84896-36-6; **39**, 84624-34-0; **40a**, 84896-37-7; *threo*-**40b**, 84896-38-8; *erythro*-**40b**, 84896-39-9; **41**, 84896-40-2; $(C_2H_5)_4NF$, 665-46-3; $(n\text{-}C_4H_9)_4NF$, 429-41-4; CsF, 13400-13-0; KF, 7789-23-3; NaF, 7681-49-4; LiF, 7789-24-4; $TiCl_4$, 7550-45-0; BTAF, 329-97-5; 2-[(trimethylsilyl)oxy]-2-(hydroxyphenylmethyl)cyclobutanone, 62248-59-3; 2-hydroxy-2-[[(trimethylsilyl)oxy]-phenylmethyl]cyclobutanone, 84896-33-3; benzaldehyde, 100-52-7; *p*-nitrobenzaldehyde, 555-16-8; isobutyraldehyde, 78-84-2; fluorotrimethylsilane, 420-56-4; *p*-anisaldehyde, 123-11-5; 2-[(4-methoxyphenyl)methylene]cyclohexanone, 5765-29-7; hexamethyldisilazane, 999-97-3; trimethylchlorosilane, 75-77-4; cyclohexanone, 108-94-1; 1-(trimethylsiloxy)cyclododecene, 51584-36-2; benzophenone, 119-61-9; 2-(1-butyl-1-hydroxypentyl)-cyclohexanone, 60599-75-9; 5-nonanone, 502-56-7; *N*-(trimethylsilyl)imidazole, 18156-74-6; phenyloxirane, 96-09-3; diethyl ethylidenemalonate, 1462-12-0; benzylacetone, 2550-26-7; benzaldehyde dimethyl acetal, 1125-88-8; 2,2-dimethyl-3-phenylpropanal, 6325-41-3; 5-(trimethylsiloxy)-2-methyl-5-phenyl-3-pentanone, 62572-36-5; methyl isopropyl ketone, 563-80-4; ethyl (trimethylsilyl)acetate, 4071-88-9; 2-methyl-5-phenyl-4-penten-3-one, 3160-32-5; cinnamaldehyde, 104-55-2; 3-phenylpropanal, 104-53-0; benzil, 134-81-6; furfural, 98-01-1; (*E*)-2-hexenal, 6728-26-3; tetrahydrofuran, 109-99-9; acetonitrile, 75-05-8; dimethoxyethane, 110-71-4; ether, 60-29-7; *N*,*N*-dimethylformamide, 68-12-2; dimethyl sulfoxide, 67-68-5.

# On the Reaction of Lithium Aluminum Hydride with Alcohols

H. Haubenstock* and T. Mester, Jr.

*Department of Chemistry, The City University of New York, The College of Staten Island, Staten Island, New York 10301*

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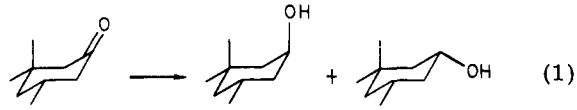
Infrared spectra of the reaction products of lithium aluminum hydride ($LiAlH_4$) with 3 molar equiv of isobutyl alcohol, 2-propanol, and the more sterically hindered 2,4-dimethyl-3-pentanol, **4**, in diethyl ether were examined. Alcohol **4** reacts with $LiAlH_4$ in diethyl ether, giving a clear solution that is highly stereoselective in the reduction of 3,3,5-trimethylcyclohexanone, **1**. The reaction of $LiAlH_4$ with **4** does not lead to tricoordinate aluminum species. On the basis of infrared spectra and the stereochemistry of reduction of **1**, it is concluded that $LiAlH_4$ is present in solution after its reaction with 3 molar equiv of isobutyl alcohol. $LiAlH_4$ is also the initial reducing species in solution after reaction with 2-propanol. On the other hand, $LiAlH_4$ reacts with methanol, ethanol, and **4**, giving lithium alkoxyaluminum hydride species. Possible pathways for the reaction of $LiAlH_4$ with alcohols are discussed.

The reaction of alcohols with lithium aluminum hydride ($LiAlH_4$) is of considerable importance although not sufficiently understood. Lithium alkoxyaluminum hydrides are intermediates in the $LiAlH_4$ reduction of carbonyl compounds. They also serve as useful selective reducing agents,[1] and many approaches to the design of chiral complex metal hydride reagents for asymmetric reductions involve the reaction of $LiAlH_4$ with chiral alcohols or phenols.[2]

The stereoselectivity of reduction (eq 1) of 3,3,5-trimethylcyclohexanone, **1**, has served as a simple probe for




(1)

**1** *trans*-**2** *cis*-**2**

the identity (or nonidentity) of lithium alkoxyaluminum hydride reducing species in solution.[3] Thus the reduction of **1** with $LiAlH_4$ in diethyl ether gave 52–55% of *trans*-**2**,[3-5] while reduction of **1** with a reagent prepared by the reaction of $LiAlH_4$ with 3 molar equiv of methanol gave 75% *trans*-**2**.[3] On the other hand, the reduction of **1** with the reagent formed from the reaction of $LiAlH_4$ with 3 molar equiv of 2-propanol gave 54–55% *trans*-**2**,[3,4] a result

Table I. Reduction of **1** with $LiAlH_4$ and Modified Reagents[a]

| entry | addend[b] | trans-axial **2**,[c] % |
|---|---|---|
| 1 | | 52–55[d] |
| 2 | $CH_3OH$ | 75[e] |
| 3 | $CH_3CH_2OH$ | 83,[e] 87[f] |
| 4 | $(CH_3)_2CH\text{-}CH_2OH$ | 57,[g] 56[h] |
| 5 | $(CH_3)_2CH\text{-}CHOH\text{-}CH(CH_3)_2$, **4** | 96[i] |

[a] In diethyl ether. [b] Three molar equivalents of addend/mole of $LiAlH_4$. [c] Preparative conditions using magnetic stirring. Alcohol epimers normalized to 100%. [d] References 3, 4. [e] Reference 3. [f] This work, 33% **1** in product. [g] Reference 4. [h] This work, 26% **1** in product. [i] This work.

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(5) This product stereochemistry was observed under small-scale preparative conditions using magnetic stirring. Under these conditions it has been reported that the actual effective reducing species are $LiAlH_4$ and the lithium monoalkoxyaluminum hydride.[6]

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