Jasco DIP 370, using a water-jacketed cell connected to the thermostat.

Racemic 2 (6.00 g, 19.1 mmol) was suspended in 100 mL of anisole (from Aldrich, used without further purification) together with 0.14 g (0.45 mmol) of (+)-2. The suspension was heated at ca. 90 °C to complete dissolution of the solid (possible undissolved particles were filtered away on fluted filter paper) and then slowly cooled in the thermostat at 40 °C. The solution showed an optical rotation α_D = +0.21 (l = 10 cm). Seeds of (+)-2 (15 mg) were added under constant stirring (100 rpm). The solution became opalescent, and crystallization of the (+)-enantiomer proceeded slowly. The optical rotation of the solution varied with time as shown in the figure. After 3 h, when α_D = −0.18/−0.20, the suspension was rapidly filtered by suction in a preheated Buchner funnel with filter paper (general-purpose filter paper with medium filtration speed; the use of fritted disks, 16–40 μm, did not allow the complete recovery of the crystals) to give, after the residue was dried under vacuum, 0.27 g of the dimethyl ether 2 with $[\alpha]_D$ = +135 (89% optical purity based on the rotation of the (+)-2 obtained from commercial (+)-1).

Racemic (±)-2 (0.27 g, 0.86 mmol) was then added to the remaining solution, which was heated at ca. 90 °C to complete dissolution of the solid (possible undissolved particles were filtered away). The solution was again thermostated at 40 °C and seeded with 15 mg of (−)-2. After 3 h, filtration and drying as above gave the (−) enantiomer. The same cycle of operation was carried out five times, yielding a total of 1.35 g of (+)-2 and 1.25 g of (−)-2 having optical purity of ca. 90% (see Table I).

A single crystallization from toluene gave 1.05 g of (+)-2 and 0.98 g of (−)-2 with optical purity >98%.

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Simple Diastereoselectivity of the Aldol Reaction of Persubstituted Enolates. Stereoselective Construction of Quaternary Centers

Shigeru Yamago, Daisuke Machii, and Eiichi Nakamura*

Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

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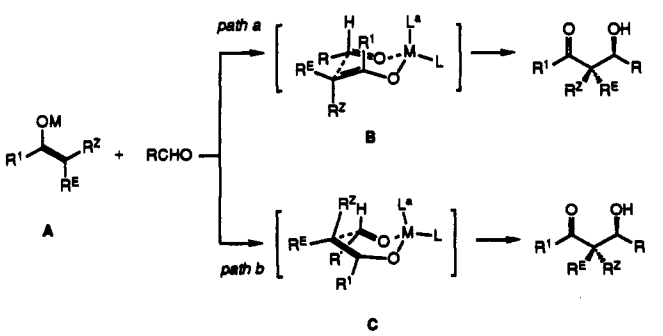
Simple diastereoselectivity of several important categories of aldol reactions of persubstituted enolates has been investigated for sterically least biased cyclic and acyclic ketone and aldehyde enolates, 1–4, and has been found to be useful for the stereoselective construction of quaternary carbon centers. The types of reactions examined involve the reaction of lithium, borinate, borate, trialkoxytitanium, trichlorotitanium, and zirconium (Cp_2ZrCl) enolates, and the reactions of enol silyl ethers under high pressure, fluoride catalysis, and Lewis acid catalysis. In contrast to the less substituted metal enolates, uncatalyzed reactions of persubstituted metal enolates proceeded in a sense anticipated from the conventional Zimmerman–Traxler chair transition state (TS) model. The fluoride-catalyzed reaction of the cyclic enolate **1a** showed stereoselectivity consistent with the open extended TS, while enolates **2a–4a** showed anomalous behavior. The selectivity of the Lewis acid mediated aldol reaction of enol silyl ethers was found to be dependent on the Lewis acid used, and the BF_3·Et_2O-mediated reaction of **2a** and **3a** showed maximum selectivity in a sense predicted by the chair TS. The stereostructures of the aldols have been determined by single-crystal X-ray analysis or by chemical correlations.

In the past decade, aldol reaction of substituted enolates with aldehydes has emerged as an extremely useful method for the stereocontrolled construction of chiral centers.[1] Through accumulated knowledge of numerous varieties of stereochemical observations, some useful inferences as to transition-state (TS) geometries[2] have been drawn on the basis of the data obtained for the reactions of trisubstituted enolates (i.e., either one of R^Z and R^E in A is hydrogen: Scheme I). The aldol reaction of persubstituted enolates (i.e., R^Z, $R^E \neq$ H) creates a quaternary carbon next to the carbonyl group and is expected to provide a powerful method for stereocontrolled construction of quaternary centers,[3,4] especially on an acyclic carbon chain. However, the potential of this promising strategy has rarely been

Scheme I



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investigated,[5-11] and correlation between the enolate geometry and the product stereochemistry in these reactions has been established only in a few reactions.[5,7b,c] Accordingly, the general validity of the standard TS models in the reactions of persubstituted enolates has yet to be thoroughly addressed.

It is also important to note that the stereochemical behavior of the persubstituted enolates will serve as a yardstick for the evaluation of the existing TS models, since, for any of them to provide truly reasonable pictures of the TSs of the aldol reaction, they must also offer rational accounts for these reactions, as well as for those of the less substituted counterparts with which they have been so successful. In fact, we have previously pointed out[11-13] that some of the conventional protocols for predicting stereoselection fail when applied to persubstituted enolates. We thus strongly felt that the stereochemistry of the aldol reaction of persubstituted enolates be investigated in detail. We describe herein the first systematic investigation of the simple diastereoselectivity of the persubstituted enolates of ketones and aldehydes possessing a variety of metal countercations. The four major categories of aldol reactions, classified according to their simple diastereoselectivity, have been examined: the reactions of metal enolates whose stereoselectivity is determined largely by the stereochemistry of the starting enolates, those which are consistently erythro-selective irrespective of the enolate geometry, the fluoride-catalyzed aldol reaction, and the Lewis acid promoted aldol reactions of the enol silyl ethers.

The aldol reaction of dialkylboron (borinate) enolates[14] represents the most important, well-defined class (referred as class I in the following text), whose diastereoselectivity is controlled by the double-bond geometry of the starting enolate.[15] Synthetically versatile lithium enolates also show similar diastereoselection.[16,17] A chairlike transition-state model (B) proposed by Zimmerman and Traxler[18] has been well accepted to account for the correlation of the E and Z geometry of the enolate to the threo and erythro stereochemistry in the aldol product (Scheme I, path a).

It was found in the early 1980s that the aldol reaction of zirconium (Cp_2ZrCl),[19] titanium,[12,20] and dialkoxyboron (borate)[21] enolates (class II) produce erythro aldols irrespective of the enolate geometry.[22] This selectivity has been rationalized by geometry-dependent change of the TS. Thus, an E enolate (R^Z = H) reacts via a boat TS to give the erythro aldol (path b), whereas a Z enolate (R^E = H) reacts via a chair TS to give the same diastereomer (path a, Scheme I). Evans et al.[19a] attributed the origin of the behavior of their zirconium enolates to the steric effect of the bulky Cp ligand on the metal. Studies on trichlorotitanium enolates,[12] on the other hand, led us to conclude that it is the intrinsic properties of these enolates that makes the E enolate prefer the boat TS.[13] This argument also implies that a boat TS may be generally favored for any metal enolate without unfavorable steric effects, and has been supported by the recent theoretical calculations on the aldol reactions of various enolates in the gas phase.[23,24] Pressure effects on the TS geometries has been recently reported for the aldol reaction of enol silyl ethers.[25]

The third category involves the enolate generated by the reaction of enol silyl ethers with a naked fluoride anion.[17a,26] In many cases, especially with sterically demanding enolates, the reaction exhibits erythro selectivity regardless of the enolate geometry, and this has been ascribed to an extended open TS (D).[27] Recent experimental[11] as well as theoretical information[23] suggests that an alternative

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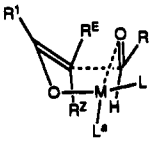

C'

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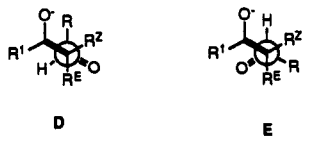
Table I. Stereoselectivity of the Aldol Reaction of Metal Enolates (eqs 2, 3)

entry	enolate	M	R	conditions	erythro:threo ($\Delta\Delta G^{\ddagger}$)[a]	% yield[b]
1	1	Li	Ph	THF/hexane, −72 °C, 5 s	9:91	86
2		BBu_2	Ph	Et_2O, −72 °C, 2 h	0.5:99.5 (2.13)	60[c]
3		BBu_2	^{n}Pr	Et_2O, −72 °C, 2 h	3:>97 (>1.40)	31[c]
4		$B(OCH_2CH_2O)$	Ph	THF/hexane/CH_2Cl_2, −72 °C, 2 h	12:88 (0.80)	57
5		$B(OMe)_2$	Ph	THF/C_6H_{12}, 4 kbar, 3 h	3:>97 (>1.40)	~50[d]
6		$Ti(OiPr)_3$	Ph	hexane, −72 °C, 1 h	5:95 (1.19)	94
7		$TiCl_3$	Ph	CH_2Cl_2, −72 °C, 5 s	12:88 (0.80)	29[c]
8		$TiCl_3$	^{n}Pr	CH_2Cl_2, −72 °C, 5 min	9:91 (0.93)	56
9		Cp_2ZrCl	Ph	THF/hexane, −72 °C, 1 h	17:83 (0.64)	56
10		$SiMe_3$	Ph	CH_2Cl_2, 50 °C, 6 days, 13 kbar	45:55 (0.13)	50
11		$SiMe_3$	^{n}Pr	CH_2Cl_2, 60 °C, 6 days, 13 kbar	43:57 (0.19)	22
12	2 (97% *Z*)	Li	Ph	THF/Et_2O, −72 °C, 10 s	45:55	76
13		BBu_2	Ph	Et_2O, −72 °C, 1.5 h, 0 °C, 0.5 h	94:6[e] (>1.11)	30
14		Cp_2ZrCl	Ph	THF/Et_2O, −72 °C, 3 h	86:14[f] (0.73)	68
15		Cp_2ZrCl	^{n}Pr	THF/Et_2O, −72 °C, 1 h	86:14[g] (0.73)	34
16	3 (86% *E*)	Li	Ph	THF/Et_2O, −72 °C, 5 s	17:83	71
17		BBu_2	Ph	Et_2O, −72 °C, 1.5 h, 0 °C, 0.5 h	3:97[h] (>1.40)	41
18		Cp_2ZrCl	Ph	THF/Et_2O, −72 °C, 3 h	9:91[i] (0.93)	56
19		Cp_2ZrCl	^{n}Pr	THF/Et_2O, −72 °C, 1 h	15:85[j] (0.70)	19
20	4 (94% *E*)	Li	Ph	THF/Et_2O, −72 °C, 5 s	40:60[k]	30
21		BBu_2	Ph	Et_2O, −72 °C, 1.5 h, 0 °C, 0.5 h	33:67[k] (>0.28)	34
22		Cp_2ZrCl	Ph	THF/Et_2O, −72 °C, 3 h	31:69[k] (0.32)	35

[a] Product ratios were determined by ^{1}H NMR except in entries 3, 8, 11, 15, and 19, wherein ratios were determined by capillary GLC. The ratios in entries 12–19 were corrected for the isomeric purity of the starting enol silyl ether (see text). The energy difference is shown only for the kinetically controlled reactions. [b] Isolated yield of the mixture of products except in entries 6, 9, 15, 19, and 20, wherein that was determined by quantitative ^{1}H NMR analysis. [c] Reference 12. [d] Reference 21b. [e] Uncorrected ratio: 91:9; [f] 84:16; [g] 84:16; [h] 18:82; [i] 22.78; [j] 27:73. [k] The ratios are uncorrected owing to the lack of the data for the *Z* enolate isomers.

open TS (E), which is energetically close to D, must also be considered for the reaction of sterically less demanding enolates.



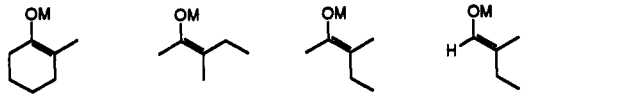
D E

Lewis acid mediated aldol reaction of enol silyl ethers[28] represents the fourth category.[29-35] Despite its remarkable power as a method for the C–C bond formation, the level and the sense of its stereoselectivity often vary, except in a single variant of the reaction,[35] that is the Me_3SiOTf-catalyzed reaction with acetals.

In the present investigation, simple diastereoselectivities of these four categories of the reactions have been examined for several representative members of persubstituted ketone and aldehyde enolates, and several useful conclusions have been drawn from the experimental observations.

Results

Generation of Enolates. Aiming at maximizing the stereoselectivity of the aldol reaction, recent studies have commonly been conducted for enolates possessing sterically demanding substituents on the organic moiety of the molecules. To the contrary, with a view to obtain information on the intrinsic properties of persubstituted metal enolates, we have chosen to examine the least sterically biased cyclic and acyclic enolates 1–4. The enolate 1,



1 2 3 4 a: M = $SiMe_3$

which has often been examined as a cyclic prototype, is readily available as its silyl ether (1a) by thermodynamic silylation of 2-methylcyclohexanone[36] followed by spinning band distillation. The *Z* and *E* enol silyl ethers **2a** and **3a**, prepared by the published procedures,[37a] differ only in the position of a methyl group; therefore, any extraneous steric effect are avoided. The former has been obtained in 97% geometrical purity, and the latter in 83–86% purity after purification by spinning band distillation. The *E* aldehyde enol silane **4** (94% geometrical purity) was prepared by stereoselective conjugate addition of Me_2CuLi to methacrolein[37c] and was examined in order to gain information on the steric effect of the α′-substituent (R^1 in A). There is currently no stereoselective way available for the preparation of the *Z* isomer of **4**.

These enol silyl ethers have been converted to lithium,[38] borinate,[14b] and trichlorotitanium[12] enolates by direct

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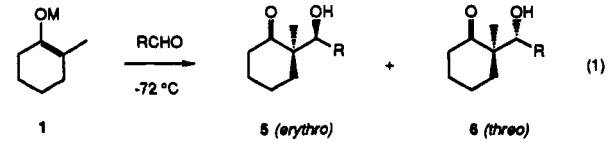
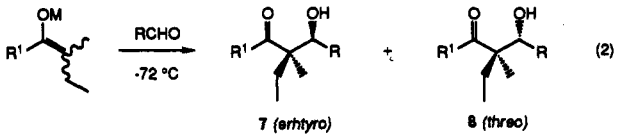
transmetalation, and to borate,[21] triisopropoxytitanium,[20] and zirconium[19] enolates by the reaction of the corresponding lithium enolate with appropriate metal chlorides in THF/hexane. The fluoride-mediated[26] and the Lewis acid mediated aldol reactions[28] have been carried out as previously described.[26a,30a]

In the present article, Noyori's erythro/threo nomenclature[27,39] for the description of the aldol products has been employed.

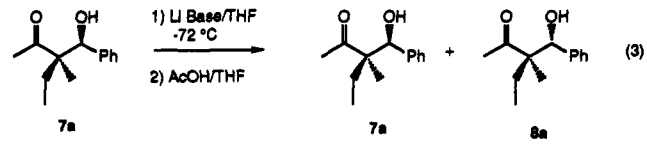
Aldol Reaction of Reactive Metal Enolates. The aldol reactions of class I and II metal enolates were examined first (eqs 1 and 2), and the results are summarized in Table I. Not unexpectedly, the tetrasubstituted enolates were often found to react more slowly than the trisubstituted counterparts. Some diastereomeric ratios have been corrected for the geometrical purity of the starting enolates assuming the equal reactivities of the *E* and *Z* enolates. This assumption appears reasonable in the light of the steric similarity of the substituents R^E and R^Z and has been borne out by the qualitative similarity of the reaction rates observed for each pair of *E* and *Z* enolates. Uncorrected values are shown as footnotes in the table.





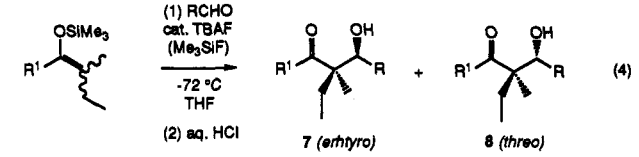
Several features are worthy of note: (1) *All* reaction showed stereoselectivity consistent with the chair TS model of the aldol reaction: the *Z* enolates gave erythro aldols and the *E* enolates threo aldols. The seemingly anomalous case in entry 12 has been shown to be due to rapid equilibration (vide infra). Thus, the class II persubstituted *E* enolates 1 and 3 exhibited a high level of threo selectivity (entries 4–9) as opposed to the erythro selectivity of the corresponding trisubstituted *E* enolates. (2) The Bu_2B borinate enolate 1 shows excellent threo selectivity (entries 2 and 3), while corresponding cyclohexanone enolate is only 67% threo selective.[15b] The aldol reaction of the borinate enolates creates quaternary centers with high diastereoselectivity (entries 2, 3, 13, and 17). (3) The reactivities of borate enolates (entries 4 and 5) have been found to be dependent on the metal ligand. Thus, dimethylborate enolate[21c] (entry 5) is inert to benzaldehyde at room temperature, while a cyclic borate (entry 4) reacted even at −72 °C. The different levels of diastereoselectivity may in part be a pressure effect. (4) Aldehyde enolate 4 shows lower threo selectivity than ketone enolates 1 and 3. (5) Unlike a cyclohexanone enolate,[25] the aldol reaction of enol silyl ether 1 under high pressure was nonselective, probably due to competing chair and boat pathways as proposed by Yamamoto.[25]

The anomalously low selectivity of the lithium enolates in entries 12 and 20 in Table I was suspected to be due to rapid equilibration.[17b,40] This expectation was borne out by appropriate control experiments (eq 3). Lithium

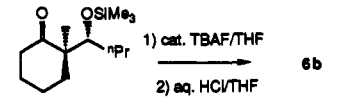


aldolate **10a** of 94% diastereomerically purity was prepared by treatment of **7a** with either BuLi or LDA, and it was quenched with acetic acid after various intervals. The aldolate underwent rapid equilibration, and the diastereomeric purity of the recovered material dropped to 72–74% even after 5 s (Table II, entries 1 and 3). The threo aldol predominated after 10 min to 1 h (entries 2 and 5). The isomerization reaction was notably faster when **10a** was prepared with BuLi. It is probable that diisopropylamine involved in an aldolate aggregate retards the isomerization. In the light of the rapid isomerization from the erythro to the threo isomer, the 45:55 ratio in entry 12 can be taken to indicate that the lithium *Z* enolate (**2**, M = Li) is also kinetically erythro-selective like other metal enolates in Table I.

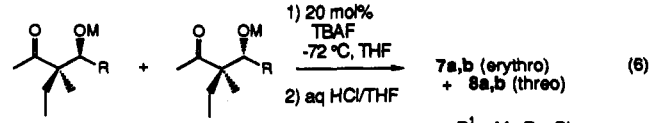
Fluoride-Catalyzed Aldol Reaction of Enol Silyl Ethers. The results of the aldol reaction of enol silyl ethers **1a–4a** (−72 °C in THF, eq 4) in the presence of tetrabutylammonium fluoride (TBAF)[11] are summarized in Table III. Strangely, the *E* and *Z* acyclic enolates **2a–4a** (entries 3–7) showed the same sense of diastereoselectivity as has been observed for the metal enolates in Table I. In contrast, the enol silyl ether of 2-methylcyclohexanone **1a** was erythro selective (entries 1 and 2), as has been expected from the conventional extended TS (D).



Although the fluoride-catalyzed aldol reaction is reversible for some specific combinations of reactants,[26c] the reactions in Table III has been confirmed to be kinetically controlled. Thus, the stereochemistry of the threo silyl aldol adduct **9**, **10**, and **11** was found to be stable under the reaction conditions (eqs 5 and 6, Table IV).



	recovery of aldol 6b
TBAF 30 mol% -78 °C 2 h	87% (98% threo)
TBAF 38 mol% -23 °C 2 h then 20 °C 1 h	54% (98% threo)



10 (erythro) 11 (threo)

a: M = Li, R = Ph
b: M = $SiMe_3$, R = Ph
c: M = $SiMe_3$, R = Pr

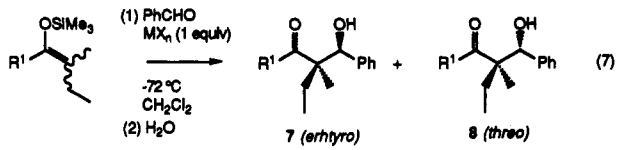
(39) For other stereochemical descriptions: (a) Masamune, S.; Ali, S. K.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. (b) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

(40) Majewski, M.; Gleave, D. M. *Tetrahedron Lett.* **1989**, *30*, 5681.

Table II. Equilibration of Lithium Aldolate 10a at −72 °C in THF (eq 3) Starting from a 94:6 Mixture of 7a and 8a

	Li base	time	7a:8a	% recovery
1	BuLi	5 s	72:28	50
2	BuLi	10 min	25:75	30
3	LDA	5 s	74:26	75
4	LDA	10 min	62:38	56
5	LDA	2 h	59:67	67

Lewis Acid Mediated Aldol Reaction. Three typical Lewis acids, $SnCl_4$, $TiCl_4$, and $BF_3{\cdot}Et_2O$, were chosen for the studies of the reaction of enol silyl ethers **1a–4a** with benzaldehyde (eq 7, Table V), and the reactions were



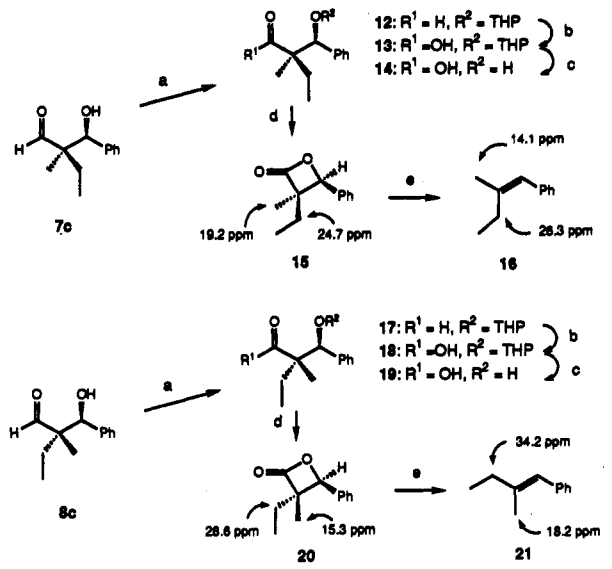
carried out as described by Heathcock.[30a] As has been often found in this reaction, the observed substrate- and reagent-dependent change of the diastereoselectivity was quite complex. The cyclic enolate **1a** gave a 1:1 mixture of diastereomers regardless of the Lewis acids used. The nature of the Lewis acid influenced little the sense of the selectivity of the acyclic ketone enolates **2a** and **3a** but exerted a great effect on the level of the diastereoselection. Thus, in the presence of $BF_3{\cdot}Et_2O$, the maximum selectivities of 84% erythro and 80% threo selectivities have been obtained for the *Z* and the *E* enolates (entries 6 and 9), respectively. It is puzzling that the sense of diastereoselection with **2a** and **3b** formally conforms to the the chair TS model. In addition, the reaction of the aldehyde *E* enolate (**4a**) was found erythro-selective, providing additional complications to the the understanding of the stereoselectivity of this reaction.

Structure Determination of the Products. The stereochemistry of the aldols obtained in the present studies cannot be determined by the conventional ^1H NMR protocol relying on the H–H coupling between protons α- and β- to the carbonyl group,[2c] since the aldol products lack the crucial α proton.

The structure of the threo aldol derived from 2-methylcyclohexanone enolate **1** and benzaldehyde has been determined by an X-ray crystal structure analysis.[41] Stereochemical assignment of the aldol obtained from **1** and butyraldehyde was made by analogy.

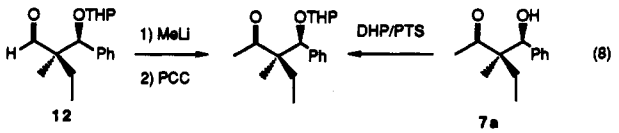
Stereostructures of the aldols obtained by the reaction of the acyclic ketone and aldehyde enolates with benzaldehyde were determined by chemical correlation. As shown in Scheme II, the threo and erythro aldehyde adducts **7c** and **8c** were converted to the corresponding acids, then to β-lactones, **15** and **20**, and finally to the trisubstituted olefins,[42] **16** and **21**, respectively. The stereostructures of the lactones and the trisubstituted olefins were assigned on the basis of the ^{13}C NMR high-field shift (steric compression effect)[43] of the starred carbons cis to the phenyl group. Correlation between the ketone adduct **7a** and the aldehyde adduct **7c** has been achieved as shown in eq 8: addition of methyllithium to the THP ether of the aldehyde adducts **12** followed by oxidation with pyridinium chlorochromate (PCC) gave a protected aldol identical by 200-MHz ^1H NMR with the THP ether of **7a**.

Scheme II[a]



[a] (a) Dihydropyran/PTS; (b) $KMnO_4$; (c) H_3O^+; (d) $PhSO_2Cl/Et_3N$; (e) 110 °C toluene.

Structures were assigned to the butyraldehyde adducts **7b** and **8b** by analogy.



Discussion

In the preceding paragraphs, we have shown that stereoselective aldol addition of persubstituted enolates represents a viable method for the synthesis of molecules possessing quaternary chiral carbon centers. Recent developments of stereoselective syntheses of persubstituted enolates[5,7-11,37] broadens the synthetic utility of this aldol route. Besides the practical utility, the diastereoselectivity of persubstituted enolates provides information about the TS of the aldol reactions.

In Table VI is summarized in the general trend of the observed diastereoselectivities of the persubstituted metal enolates (entries 3–5), together with the data for the corresponding trisubstituted ones (entries 1 and 2).[2c] For the class I enolates both tri- and persubstituted enolates react via the classical Zimmerman–Traxler TS regardless of the enolate geometry. In the reaction of the class II enolates, on the other hand, tri- and persubstituted enolates show different stereochemical behavior. Thus, while the former gives erythro aldols regardless of the enolate geometry, the latter conforms to the conventional Zimmermann–Traxel protocol. We believe, as proposed earlier,[12,13] that this is testimony that the substituent R^Z (when $R^Z \neq H$) cis to the enolate oxygen destabilizes the boat TS relative to the chair TS. Therefore, the results may be summarized that every enolate possessing $R^Z \neq H$, irrespective of its formal *E,Z* geometry, reacts via a chair TS. The reason behind the effect of R^Z may be related to the conformation of the starting metal enolates[24] and/or to the interactions in the TS.[23] Houk's recent ab initio calculations quantitatively confirmed the destabilizing effect of R^Z in the TS.

The implication of the R^Z effect may be also useful to understand the observed levels of the selectivity of the class I enolates in general. We have previously suggested that the generally lower selectivity of class I, *E* enolates is due to erosion of the chair preference itself (i.e., leak to the boat

(41) Nakamura, E.; Kuwajima, I.; Willard, P. G. *Acta Crystallogr. C*, in press.
(42) Adam, W.; Baeza, J.; Liu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000.
(43) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd ed.; Verlag Chemie: Wheinheim, 1987.

Table III. TBAF-Catalyzed Aldol Reaction of Enol Silyl Ethers

entry	enol silyl ether	R	TBAF (mol %)	time (h)	erythro:threo 7:8 ($\Delta\Delta G^{\ddagger}$)	% yield
1	**1a**	^{n}Pr	15	2	86:14 (0.73)	49
2[a]	**1a**	^{n}Pr	28	15	88:12 (0.80)	30
3	**2a** (97% *Z*)	Ph	20	0.5	64:36[b,c] (0.23)	97
4	**2a**	^{n}Pr	20	2	68:32[b,d] (0.30)	60
5	**3a** (83% *E*)	Ph	20	0.5	29:71[b,e] (0.36)	68
6	**4a** (94% *E*)	^{n}Pr	20	2	22:78[b,f] (0.51)	65
7	**4a**	Ph	20	2	35:65 (0.25)	68

[a] Carried out in the presence of 5 equiv of Me_3SiF. [b] Corrected for the isomeric purity of the starting enol silyl ethers (see text). [c] Uncorrected ratio: [c] *63*:37; [d] *67*:33; [e] *35*:65; [f] *30*:70.

Table IV. Configurational Stability of the Silyl Aldols in the Presence of TBAF at −72 °C (eq 6)

silyl aldol (10:11)	% recovery (as aldols 7 and 8)	7:8
R = Ph **b** (94:6)	60	90:10
R = Ph **b** (9:91)	87	11:89
R = ^{n}Pr **c** (98:2)	53	93:7
R = ^{n}Pr **c** (23:77)	41	15:85

Table V. Stereochemistry of the Lewis Acid Mediated Aldol Reaction

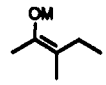
entry	enol silyl ether	Lewis acid	erythro:threo ($\Delta\Delta G^{\ddagger}$)	% yield
1	**1a**	$SnCl_4$	58:42 (0.03)	73
2	**1a**	$TiCl_4$	58:42 (0.03)	84
3	**1a**	$BF_3{\cdot}Et_2O$	48:52 (0.03)	80
4	**2a** (97% *Z*)	$SnCl_4$	56:44[a,b] (0.10)	50
5	**2a**	$TiCl_4$	68:32[a,c] (0.30)	67
6	**2a**	$BF_3{\cdot}Et_2O$	84:16[a,d] (0.67)	89
7	**3a** (83% *E*)	$SnCl_4$	48:52[a,e] (0.03)	76
8	**3a**	$TiCl_4$	33:67[a,f] (0.28)	86
9	**3a**	$BF_3{\cdot}Et_2O$	20:80[a,g] (0.56)	84
10	**4a** (94% *E*)	$SnCl_4$	77:23 (0.48)	74
11	**4a**	$TiCl_4$	55:45 (0.08)	34
12	**4a**	$BF_3{\cdot}Et_2O$	76:24 (0.46)	64

[a] Corrected for the isomeric purity of the starting enol silyl ethers. [b] Uncorrected ratio: [b] 56:44; [c] 67:33; [d] 84:16; [e] 49:51; [f] 39:61; [g] 31:69.

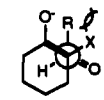
TS) rather than the "looseness" of the chair TS. The Houk calculations[23] supported this view by showing that the the boat preference of a prototype BH_2 borinate enolates erodes in the presence of either R^Z or an axial ligand on the boron atom. The sharp contrast between the excellent threo selectivity with Bu_2B borinate enolate **1** (≥99% threo) and the poor selectivity with the cyclohexanone enolate (76% threo)[15b] attests to the large steric effect of R^Z. In other words, for a given metal countercation, the aldol reaction of persubstituted enolates would more rigorously conform to the chair TS than the less substituted enolate and should be generally useful for the stereoselective synthesis of quaternary centers.

The present studies have confirmed that the size of the α'-substituent R^1 affects the diastereoselectivity. Occupying a pseudo-axial position, the enolate ligand R^1 in the Zimmerman–Traxler TS (B) confers enhanced diastereoselection. It follows therefore that stereoselectivity should decrease in the reaction of aldehyde enolates even in the presence of R^Z. All aldehyde metal enolates **4** examined indeed showed lower threo-selectivity than the corresponding ketone enolates (Table I, entries 20–22). In a related, yet contrasting context, enhanced diastereoselectivity of ketone enolates having bulky α'-substituents (e.g., R^1 = *tert*-butyl) has been established.[17,44] The Houk calculations[23b] also supported these experimental observations.

Table VI. Stereoselectivity of the Aldol Reaction of Metal Enolates

entry	enolate (general structure)	M = Li, BBu_2 (class I)	M = $B(OR)_2$, TiX_3, Cp_2ZrCl (class II)
1	 (*Z*)	erythro	erythro
2	 (*E*)	threo	erythro
3	 (*Z*)	erythro	erythro
4	 (*E*)	threo	threo
5	 (*E*)	threo	threo

The erythro-selective fluoride-catalyzed reaction of the enol silyl ether of 2-methylcyclohexanone (**1a**) (Table III, entries 1 and 2) is consistent with the open extended TS (F, X = Me).[27,45] The 2-methyl group exerts gauche steric



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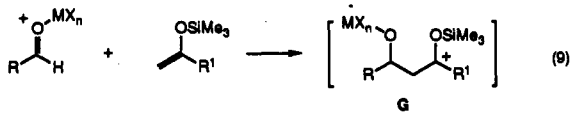
effect with the R group of the aldehyde, thereby lowering the selectivity relative to the unsubstituted cycohexanone enolate (X = H). The behavior of the acyclic enol silyl ethers **3a–5a**, however, cannot be rationalized by such extended TS (Table II, entries 3–7). In view of the evidence against cyclic TSs presented elsewhere,[11] the observed *E*→threo/*Z*→erythro selectivity is likely to be due to contribution of an additional open TS, skew TS (E) (vide supra). Detailed discussion of the contribution of these diastereomeric TSs D and E, however, must presently remain too speculative. A practical advantage of the fluoride methodology resides in its erythro selectivity of the cyclic enolate **1**, which is complementary to the threo selectivity of the corresponding metal enolates (Table I, entries 1–9).

The Lewis acid mediated reactions of persubstituted enol silyl ethers showed a stereochemically complex behavior. Nevertheless, they excelled in yield relative to other aldol reactions, and often showed acceptable levels of stereoselectivity. The aldol reaction of acyclic enol silyl ethers **2a** and **3a**, especially the BF_3-mediated reaction (Table V), calls for the chair TS. However, it is difficult

(44) Bloch, B.; Gilbert, L. *Tetrahedron Lett.* **1986**, *30*, 3511.

(45) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8032.

to find reasons why BF_3, with its smaller number of vacant coordination sites and with less acidity, could make a more ordered chair TS than other two Lewis acids. Further complication arises from the stereochemical reversal on going from the ketone *E* enolate (3) to the aldehyde *E* enolate (4). It is probable that the reaction mechanism vary as the Lewis acid and the structure of the enol silyl ether are varied. For instance, stabilization of the putative cationic intermediate G would be much less for aldehyde enol silyl ethers than for ketone counterparts, and would consequently affect the selectivity of the reaction. It may also be relevant to note that the BF_3-mediated reaction predominantly affords silylated aldols, while $TiCl_4$-mediated one gives titanium aldolates (^1H NMR analysis). It is clear that the Lewis acid changes the mechanistic details, though the overall mechanistic framework may remain the same.



(9)

Conclusion. The aldol reaction of persubstituted enolates often show simple diastereoselectivity better defined than that of the trisubstituted enolates. It is particularly notable that *all reactive metal enolates examined conformed to the Zimmerman–Traxler TS model regardless of the identity of the metal atom.* This stands in contrast to the chemistry of less substituted metal enolates, among which *E* isomers of some metal enolates react via a boat TS. Destabilization of the boat TS by the presence of R^Z in the persubstituted enolates is probably the reason behind this experimental observation. It is also in good accordance with the recent theoretical calculations for the aldol reactions in the gas phase. The fluoride-catalyzed and the Lewis acid catalyzed reactions have been found to exhibit much less defined stereochemical behavior. The Lewis acid mediated reaction, however, provides a reliable high-yield process with reasonable selectivity, and have good practical synthetic utility for the synthesis of quaternary carbon centers. In summary, combined use of these reaction conditions enables the synthesis of both of the two possible diastereomers of α,α'-dialkyl-β-hydroxy ketones and aldehydes in good to excellent selectivity with predictable stereochemistry.

Experimental Section

General. All reaction conditions dealing with air- and moisture-sensitive compounds were carried out in a dry reaction vessel under nitrogen. Liquid samples were introduced either neat via a microsyringe or in an organic solvent via a hypodermic syringe. Solid samples were weighed into a vessel in a nitrogen-filled bag. Routine chromatography was performed on silica gel using ethyl acetate and hexane as eluant. Medium-pressure liquid chromatography (MPLC) was performed on a Merck Lober column under pressure using the same solvent mixture.

IR spectra were recorded on Hitachi 260-10 or JASCO IR-800 instrument; absorptions are reported in cm^{-1}. ^1H NMR spectra was taken at 60 MHz on Hiatchi R-24B instrument, and at 200 MHz on JEOL FX-200 instrument, which was also used for ^{13}C NMR spectra at 50 MHz. Spectra are reported in part per million from internal tetramethylsilane. Gas chromatographic analysis was performed on a Shimadzu 4BM machine equipped with a OV-1 (25 m) or OV-17 (25 m) glass capillary column. High-resolution mass spectra was obtained from a Shimazu 9020-DF GC/MS system equipped with an OV-1 (7 m) capillary column. Microanalysis were performed on a Perkin-Elmer 240 instrument.

Material. Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Ethereal solvents were distilled from benzophenone ketyl immediately under nitrogen before use. Acetonitrile and methylene chloride were distilled successively from P_2O_5 and K_2CO_3 and stored over molecular sieves. Hexane was distilled from $LiAlH_4$ under nitrogen and stored over potassium mirror. Chlorotrimethylsilane and hexamethylphosphoric triamide (HMPA) were distilled from CaH_2, and stored over CaH_2 and molecular sieves, respectively. $CuBr{\cdot}Me_2S$ complex was prepared as described[46] and stored under nitrogen.

$TiCl_4$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ were distilled under nitrogen and stored under nitrogen. $ZrCl_2Cp$ was sublimed under reduced pressure and stored under nitrogen. Di-*n*-butylboryl trifluoromethanesulfonate (Bu_2OTf) was prepared as described[15b] and used immediately. Triisopropoxytitinium chloride was prepared as described[20] and used as a 1.64 M hexane solution. Boryl chloride was prepared as described[21c] and used as a ca. 4 M methylene chloride solution. Tetrabutylammonium fluoride (TBAF), which is available as the trihydrate (Aldrich), was dried over P_2O_5 (30–40 °C, 0.5 mmHg, over night) and used as it was or as a THF solution. Fluorotrimethylsilane was prepared as described[47] and used as a ca. 5 M hexane solution. Carbonyl compounds were distilled before use.

Enol Silyl Ethers: 2-Methyl-1-(trimethylsiloxy)-1-cyclohexene (1). The product obtained by silylation of 2-methylcyclohexanone with $Me_3SiCl/NaI/Et_3N$ in CH_3CN[36a] was purified by distillation through a spinning-band column to obtain a sample of 96% isomeric purity (83 °C (21 mmHg); GLC analysis on OV-1, 110 °C).

(*Z*)-3-Methyl-2-(trimethylsiloxy)-2-pentene (2). Enol silyl ether 2 was prepared from tiglic acid by a published procedure.[37a] Isomeric purity of 2 was 97% as judged by GLC analysis (OV-17, 100 °C).

(*E*)-3-Methyl-2-(trimethylsiloxy)-2-pentene (3).[37c] To a stirred suspension of 7.4 g of $CuBr{\cdot}Me_2S$ (36 mmol) in 240 mL of THF was added 45 mL of MeLi (72 mmol, 1.6 M in ether) at 0 °C. After being stirred for 15 min at this temperature, the reaction mixture was cooled to −72 °C, and 21.5 g of HMPA (120 mmol) in 20 mL of THF was added followed by 5.1 g of 3-methylbuten-2-one (60 mmol) and 13.0 g of chlorotrimethylsilane (120 mmol) over 40 min. The resulting solution was stirred for 2 h at this temperature and was gradually warmed to room temperature over 2 h. Triethylamine (12.1 g, 120 mmol), 0.3 mL of a pH 7.4 phosphate buffer, and 500 mL of pentane were added, and the reaction mixture was filtered though a pad of Celite, and the filtrate was washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the oily product was purified by distillation to obtain a sample of 72% isomeric purity (bp 130–159 °C; GLC analysis on OV-17 100 °C). The oil was purified by distillation though a spinning-band column to obtain a sample of 86% isomeric purity (GLC analysis on OV-17).

(*E*)-2-Methyl-1-(trimethylsiloxy)-1-butene (4).[37a] To a stirred suspension of 1.0 g of $CuBr{\cdot}Me_2S$ (5 mmol) in 100 mL of THF was added a 2.9 M ether solution of MeMgBr (21 mL, 60 mmol) and 17.9 g of HMPA (100 mmol) at −72 °C. To this solution was added a mixture of 3.5 g of methacrolein (50 mmol) and 10.9 g of chlorotrimethylsilane (100 mmol) in 40 mL of THF over 1.5 h at −72 °C. The resulting solution was gradually warmed to room temperature over 15 h, diluted with pentane, and quenched by addition of ca. 1 mL of a pH 7.4 phosphate buffer. The reaction mixture was filtered though a pad of Celite, and the filtrate was washed with water, 1 N HCl, saturated aqueous $NaHCO_3$, and saturated brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the oily product was purified by distillation (120–134 °C) to obtain a 5.2 g of 4 as colorless liquid in 66% yield. Isomeric purity of 4 was 94% as judged by GLC analysis (OV-1, 90 °C): IR (neat) 1665, 1225, 1168, 878, 842; ^1H NMR (200 MHz, $CDCl_3$) 0.16 (s, 9 H), 0.97 (t, J = 2.1 Hz, 3 H), 1.59 (s, 3 H), 1.89 (q, J = 2.1 Hz, 3 H), 6.01 (s, 1 H).

General Procedure of the Aldol Reaction. Aldol Reaction of Dibutylboron Enolate with Benzaldehyde. To a solution of 60.3 mg of Bu_2OTf (0.22 mmol) in 0.5 mL of ether was added

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43.1 mg of (*E*)-3-methyl-2-(trimethylsiloxy)-2-pentene (**3**) (0.25 mmol, 83% *E*) at −72 °C, and the solution was allowed to warm to 0 °C and was stirred for 20 min at this temperature. Volatile materials were removed in vacuo at room temperature, and 0.5 mL of ether was introduced. The solution was cooled to −72 °C, and 21.2 mg of benzaldehyde (0.2 mmol) was added. After being stirred at this temperature for 1 h, the solution was allowed to warm to 0 °C over 0.5 h. The resulting solution was quenched by addition of 4 mL of a pH 7.4 phosphate buffer. After the solution was extracted with ether, the combined organic extracts were concentrated in vacuo, and the crude oily product was treated with 0.2 mL of 30% H_2O_2 in 0.6 mL of MeOH for 2 h. After usual workup (extraction with ether, washing extracts with saturated $NaHCO_3$ and brine, drying over $MgSO_4$, and concentration in vacuo), the crude oily product (46.4 mg) obtained was subjected to ^1H NMR analysis; the aldol products were formed as a 82:18 of the threo and erythro isomer. Silica gel chromatography (10% ethyl acetate/hexane) afforded the aldol products in 41% yield (16.9 mg, 0.08 mmol) as a mixture of the isomers.

(3*RS*,1′*RS*)-3-((Hydroxyphenyl)methyl)-3-methylpentan-2-one (7a): IR (neat) 3450, 1695, 1490, 1455, 1420, 1380, 1355, 1220, 1125, 1085, 1055, 1020, 960, 900, 760, 705, 640, 585; ^1H NMR (200 MHz, $CDCl_3$) 0.87 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 1.10 (s, 3 H, CH_3), 1.35–1.60 (m, 1 H, CH_2CH_3), 1.85–2.10 (m, 1 H, CH_2CH_3), 2.08 (s, 3 H, $COCH_3$), 2.85 (d, J = 3.0 Hz, 1 H, OH), 4.86 (d, J = 3.0 Hz, 1 H, CHOH), 7.31 (s, 5 H, C_6H_5); ^{13}C NMR (50 MHz, $CDCl_3$) 8.3 (q), 16.8 (q), 26.3 (t), 27.4 (q), 55.2 (s), 77.4 (d), 126.5 (d), 126.6 (d), 126.7 (d), 139.5 (s), 214.0 (s). Anal. ($C_{13}H_{18}O_2$): C, H.

(3*RS*,1′*SR*)-3-((Hydroxyphenyl)methyl)-3-methylpentan-2-one (8a): IR ($CHCl_3$) 3610, 3480, 1700, 1495, 1460, 1420, 1385, 1355, 1125, 1085, 1060, 1040, 1020, 1005, 960, 895, 585; ^1H NMR (200 MHz, $CDCl_3$) 0.80 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 1.09 (s, 3 H, CH_3), 1.15–1.40 (m, 1 H, CH_2CH_3), 1.60–1.85 (m, 1 H, CH_2CH_3), 2.22 (s, 3 H, $COCH_3$), 2.73 (d, J = 4.1 Hz, 1 H, OH), 4.95 (d, J = 4.1 Hz, 1 H, CHOH), 7.31 (s, 5 H, C_6H_5); ^{13}C NMR (50 MHz, $CDCl_3$) 8.7 (q), 15.3 (q), 27.7 (q), 29.7 (t), 56.4 (s), 78.2 (d), 127.6–127.8 (d, overlapping three signals), 140.5 (s), 215.0 (s). Anal. ($C_{13}H_{18}O_2$): C, H.

Aldol Reaction of Lithium Enolate with Benzaldehyde. To a solution of 203 mg of 2-methyl-1-(trimethylsiloxy)cyclohexene (1) (1.1 mmol) in 2 mL of THF was added a 1.53 M hexane solution of BuLi (0.72 mL, 1.1 mmol) at 0 °C, and the solution was stirred for 30 min. The solution was cooled to −72 °C, and 106 mg of benzaldehyde (106 mg, 1.0 mmol) was added. After the solution was stirred for 5 s, 0.7 mL of 10% v/v of acetic acid in THF followed by saturated aqueous sodium bicarbonate was added and the mixture was allowed to warm room temperature. After usual workup, oily crude product was obtained (299 mg). The crude oil product was subjected to ^1H NMR analysis; the aldol products were formed as a 91:9 of the threo and erythro isomer. Silica gel chromatography (17% ethyl acetate/hexane) afforded the aldol products in 86% yield (188 mg, 0.86 mmol).

(2*RS*,1′*RS*)-2-((Hydroxyphenyl)methyl)-2-methylcyclohexanone (5a): IR (neat) 3425 (br), 1700, 1450, 1045, 705; ^1H NMR (200 MHz, $CDCl_3$) 1.07 (s, 3 H, CH_3), 1.20–2.71 (m, 8 H), 3.08 (d, J = 3.4 Hz, 1 H, OH), 5.08 (d, J = 3.4 Hz, 1 H, CHOH), 7.29 (s, 5 H, C_6H_5). Anal. ($C_{14}H_{18}O_2$): C, H.

(2*RS*,1′*SR*)-2-((Hydroxyphenyl)methyl)-2-methylcyclohexanone (6a): IR (CCl_4) 3510, 1690, 1450, 1040, 710; ^1H NMR (200 MHz, $CDCl_3$) 1.18 (s, 3 H, CH_3), 1.47–1.86 (m, 5 H), 1.86–2.10 (m, 1 H), 2.29–2.46 (m, 1 H), 2.63–2.71 (m, 1 H), 3.97 (br s, 1 H, OH), 4.97 (br s, 1 H, CHOH), 7.31 (s. 5 H, C_6H_5). Anal. ($C_{14}H_{18}O_2$): C, H.

Aldol Reaction of a Borate Enolate with Benzaldehyde. To a solution of 36.9 mg of 2-methyl-1-(trimethylsiloxy)cyclohexene (1) (0.2 mmol) in 0.2 mL of THF was added a 1.51 M hexane solution of BuLi (132 μL, 0.2 m mmol) at 0 °C, and the solution was stirred for 30 min. The solution was cooled to −72 °C, and a 4 M CH_2Cl_2 solution of $(OCH_2CH_2O)BCl$ (55 μL, 0.22 mmol) was added, and the solution was stirred for 2 h. Benzaldehyde (21.2 mg, 0.2 mmol) was added. After being stirred for 30 min, the solution was quenched by addition of triethanolamine (40 μL) and water (1 mL) and was stirred for 30 min. After usual workup, oily crude product was obtained (46 mg). Tetrachloroethane was added, and this mixture was analyzed by ^1H NMR to estimate the yield of the aldol products as 57% yield (threo:erythro = 88:12).

Aldol Reaction of Triisopropoxytitanium Enolate with Benzaldehyde. To a solution of 203 mg of 2-methyl-1-(trimethylsiloxy)cyclohexene (1) (1.1 mmol) in 2 mL of THF was added a 1.53 M hexane solution of BuLi (0.72 mL, 1.1 mmol) at 0 °C, and the solution was stirred for 30 min. The solution was cooled to −72 °C, a 1.64 M hexane solution of $TiCl(O^iPr_3)$ (0.67 mL, 1.1 mmol) was added, and the solution was stirred for 2 h. Solvent was removed in vacuo (at −72 to 25 °C), 2 mL of hexane was added, and the solution was cooled to −72 °C. Benzaldehyde (106 mg, 1.0 mmol) was added, and the solution was stirred for 1 h. The reaction was quenched by consecutive addition of ca. 5 mL of saturated NH_4F and 3 mL of ether, and the resulting solution was stirred for 30 min at room temperature. After usual workup, oily crude product was obtained (313 mg). The crude oil product was subjected to ^1H NMR analysis; the aldol products were formed as 95:5 of the threo and erythro isomer. Silica gel chromatography (17% ethyl acetate/hexane) afforded a diastereomeric mixture of the aldol products in 94% yield (206 mg, 0.94 mmol).

Aldol Reaction of Trichlorotitanium Enolate with *n*-Butyraldehyde. To a solution of 553 mg of 2-methyl-1-(trimethylsiloxy)cyclohexene (1) (3.0 mmol) in 6.6 mL of CH_2Cl_2 was added a 568 mg of $TiCl_4$ (3.0 mmol) at room temperature, and this solution was stirred for 30 min. The solution was cooled to −72 °C, and 324 mg of *n*-butyraldehyde (4.5 mmol) was added. After being stirred for 5 min, the solution was quenched by addition of water (3 mL). After usual workup, oily crude product was obtained (530 mg). The crude oil product was subjected to GLC analysis; the aldol products were formed as 91:9 mixture of the threo and the erythro isomer (OV-1, 150 °C). Silica gel chromatography (10% ethyl acetate/hexane) afforded the aldol products in 56% yield (313 mg, 1.7 mmol).

(2*RS*,1′*RS*)-2-((Hydroxypropyl)methyl)-2-methylcyclohexanone (5b): IR (neat) 3430 (br), 1690, 1450, 1115; ^1H NMR (200 MHz, $CDCl_3$) 0.93 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.11 (s, 3 H, CH_3), 1.17–2.09 (m, 10 H), 2.16–2.34 (m, 1 H), 2.41–2.61 (m, 1 H), 2.48 (d, J = 5.3 Hz, 1 H, OH), 3.77–3.90 (m, 1 H, CHOH). Anal. ($C_{11}H_{20}O_2$): C, H.

(2*RS*,1′*SR*)-2-((Hydroxypropyl)methyl)-2-methylcyclohexanone (6b): IR (neat) 3425 (br), 1700, 1455, 1120; ^1H NMR (200 MHz, $CDCl_3$) 0.93 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.17 (s, 3 H, CH_3), 1.22–2.08 (m, 10 H), 2.20–2.37 (m, 1 H), 2.41–2.65 (m, 1 H), 3.32 (d, J = 3.6 Hz, 1 H, OH), 3.71–3.86 (m, 1 H, CHOH). Anal. ($C_{11}H_{20}O_2$): C, H.

Aldol Reaction of $ZrCp_2Cl$ Enolate with Benzaldehyde. To a solution of 9.5 mg of (*E*)-2-(trimethylsiloxy)-3-methyl-2-pentene (**3**) (0.055 mmol, 83% *E*) in 0.15 mL of THF was added a 1.57 M ether solution of MeLi (34 μL, 0.053 mmol) at 0 °C. The solution was cooled to −72 °C, and a 0.46 mL of THF solution of 17.0 mg of $ZrCl_2Cp_2$ (0.058 mmol) was added, and the solution was stirred for 1 h at room temperature. The solution was cooled to −72 °C, and 5.3 mg of benzaldehyde (0.050 mmol) was added. After being stirred for 3 h, the solution was quenched by addition of 0.1 mL of saturated NH_4Cl. After the precipitates were removed by passing through a pad of Celite, usual workup afforded a crude oil (15.6 mg). The crude oil was subjected to ^1H NMR analysis; the aldol products were formed as a 78:22 mixture of the threo and erythro isomer. Silica gel chromatography (15% ethyl acetate/hexane) afforded the aldol products in 56% yield (5.8 mg, 0.028 mmol).

Duplication of the reaction using using 203 mg of 2-methyl-1-(trimethylsiloxy)cyclohexene (1) (1.1 mmol), 0.72 mL of 1.53 M BuLi in hexane (1.1 mmol), 323 mg of Cp_2ZrCl_2 (1.1 mmol), and 106 mg of benzaldehyde (1.0 mmol) afforded the aldol products **5a** and **5b** in 56% yield (121 mg, 0.56 mmol).

Aldol Reaction Enol Silyl Ether with Benzaldehyde under High Pressure. A solution of 184 mg of 2-methyl-1-(trimethylsiloxy)cyclohexene (1) (1.0 mmol) and 106 mg of benzaldehyde (1.0 mmol) in 1.64 mL of CH_2Cl_2 in a Teflon vessel was pressurized at 13 kbar of hydrostatic pressure for 6 days at 50 °C. The reaction was cooled and depressurized, and solvents were removed in vacuo. The crude products were stirred with 0.2 mL of 1 N HCl in 4 mL of THF for 1 h at room temperature. After usual workup, oil crude product was obtained (212 mg). The crude

product was subjected to ^1H NMR analysis; the aldol products were formed as a 55:45 of the threo and erythro isomer. Silica gel chromatography (16% ethyl acetate/hexane) afforded the aldol products in 50% yield (109 mg, 0.50 mmol).

Fluoride-Catalyzed Aldol Reaction of Enol Silyl Ether with *n*-Butyraldehyde. To a solution of 3.6 mg of *n*-butyraldehyde (0.05 mmol) and 3.1 mg of TBAF (0.01 mmol) in 0.3 mL of THF was added 9.5 mg of (*E*)-3-methyl-2-(trimethylsiloxy)-2-pentene (3) (0.055 mmol) at −72 °C. After being stirred for 2 h, the solution was quenched by addition of 0.1 mL of water. The solution was extracted with ether, the extracts were dried over $MgSO_4$, and solvent was removed in vacuo. The crude oil was treated with 30% v/v of 1 N HCl in THF for 15 min at room temperature. After usual workup, an oily product was obtained (6.2 mg). The crude product was subjected to GLC analysis; the aldol products were formed as 60:40 of the threo and erythro isomr (OV-17, 130 °C). Silica gel chromatography (15% ethyl acetate/hexane) afforded the aldol products in 65% yield (5.6 mg, 0.03 mmol).

(3*RS*,1′*RS*)-3-Ethyl-4-hydroxy-3-methylheptan-2-one (7b): IR (neat) 3425, 1700, 1465, 1420, 1385, 1360, 1225, 1115, 1080, 1015, 975, 900, 855, 785, 590; ^1H NMR (200 MHz, $CDCl_3$) 0.83 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 0.92 (t, J = 7.0 Hz, 3 H, $(CH_2)_2CH_3$), 1.11 (s, 3 H, CH_3), 1.2–1.9 (m, 7 H), 2.13 (s, 3 H, $COCH_3$), 3.73 (dd, J = 9.6, 2.4 Hz, 1 H, CHOH). Anal. ($C_{10}H_{20}O_2$): C, H.

(3*RS*,1′*SR*)-3-Ethyl-4-hydroxy-3-methylheptan-2-one (8b): IR (neat) 3430, 1700, 1465, 1420, 1385, 1360, 1285, 1225, 1100, 1080, 1010, 975, 900, 850, 785, 705, 580; ^1H NMR (200 MHz, $CDCl_3$) d 0.80 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 0.95 (t, J = 6.9 Hz, 3 H, $(CH_2)_2CH_3$), 1.12 (s, 3 H, CH_3), 1.2–1.9 (m, 7 H), 2.16 (s, 3 H, $COCH_3$), 3.77 (dd, J = 9.7, 1.7 Hz, 1 H, CHOH). Anal. ($C_{10}H_{20}O_2$): C, H.

Fluoride-Catalyzed Aldol Reaction in the Presence of TMSF. To a solution of 144 mg of *n*-butyraldehyde (2.0 mmol) and 177 mg of TBAF (0.56 mmol) in 2 mL of THF was added 2.0 mL of 4.97 M hexane solution of TMSF (10 mmol) at 0 °C, and the solution was cooled to −100 °C. 2-Methyl-1-(trimethylsiloxy)cyclohexene (1) (406 mg, 2.2 mmol) was added, and the solution was warmed to −72 °C and was stirred for 15 h. The reaction was quenched by addition of 10 mL of hexane followed by 4 mL of water. The water layer was extracted with ether, the combined extracts were dried over $MgSO_4$, and solvent was removed in vacuo. The crude oil was treated with 4 mL of 30% v/v of 1 N HCl in THF for 20 min at room temperature. After usual workup, an oily product was obtained (238 mg). The crude product was subjected to ^1H NMR analysis; the aldol products were formed as 12:88 of the threo and erythro isomer. Silica gel chromatography (13% ethyl acetate/hexane) afforded the aldol products in 30% yield (109 mg, 0.59 mmol).

$SnCl_4$-Mediated Aldol Reaction of Enol Silyl Ether with Benzaldehyde. To a solution of 10.6 mg of benzaldehyde (0.10 mmol) and 26.1 mg of $SnCl_4$ (0.10 mmol) in 0.4 mL of CH_2Cl_2 was added 20.7 mg of (*E*)-2-methyl-1-(trimethylsiloxy)-2-pentene (3) (0.12 mmol) at −72 °C. After being stirred for 4 h, the solution was quenched by addition of 0.25 mL of saturated $NaHCO_3$. After usual work up, oily product was obtained (21 mg). The crude product was subjected to ^1H NMR analysis; the aldol product was formed as a 51:49 of the threo and erythro isomer. Silica gel chromatography (14% ethyl acetate/hexane) afforded the aldol product in 75% yield (15.4 mg, 0.08 mmol).

$TiCl_4$-Mediated Aldol Reaction of Enol Silyl Ether with Benzaldehyde. To a solution of 44.2 mg of 2-methyl-1-(trimethylsiloxy)cyclohexene (1) (0.24 mmol) and 21.2 mg of benzaldehyde (0.20 mmol) in 0.8 mL of CH_2Cl_2 was added 37.9 mg of $TiCl_4$ (0.20 mmol) at −72 °C. After being stirred for 4 h, the solution was quenched by addition of 0.5 mL of saturated $NaHCO_3$. After usual workup, oily product was obtained (50.1 mg). The crude product was subjected to ^1H NMR analysis; the aldol product was formed as a 40:60 of the threo and erythro isomer. Silica gel chromatography (13% ethyl aceate/hexane) afforded the aldol product in 88% yield (38.3 mg, 0.18 mmol).

BF_3·OEt_2-Mediated Aldol Reaction of Enol Silyl Ether with Benzaldehyde. To a solution of 10.6 mg of benzaldehyde (0.10 mmol) and 14.2 mg of BF_3·OEt_2 (0.10 mmol) in 0.4 mL of CH_2Cl_2 was added 19.0 mg of (*E*)-2-methyl-1-(trimethylsiloxy)-1-butene (4) at −72 °C. After being stirred for 4 h, the solution was quenched by addition of 0.25 mL of saturated $NaHCO_3$. The solution was extracted with ether, and the extracts were dried over $MgSO_4$, and solvent was removed in vacuo. The crude oil was treated with 0.2 mL of 30% v/v of 1 N HCl in THF for 30 min at room temperature. After usual workup, the crude product was subjected to ^1H NMR analysis; the aldol product was formed as a 21:79 of the threo and erythro isomer. Silica gel chromatography (10% ethyl acetate/hexane) afforded the aldol product in 64% yield (12.2 mg, 0.06 mmol).

(2*RS*,1′*RS*)-1-((Hydroxyphenyl)methyl)-2-methyl-1-butanal (7c): IR (neat) 3400, 1725, 1500, 1460, 1385, 1205, 1270, 1110, 1090, 1040, 980, 915, 780, 740, 710; ^1H NMR (200 MHz, $CDCl_3$) 0.85 (t, 3 H, J = 7.6 Hz, CH_2CH_3), 1.06 (s, 3 H, CH_3), 1.1–1.8 (m, 2 H, CH_2CH_3), 4.85 (s, 1 H, CHOH), 7.32 (s, 5 H, C_6H_5), 9.71 (s, 1 H, CHO).

(2*RS*,1′*SR*)-1-((Hydroxyphenyl)methyl)-2-methyl-1-butanal (8c): IR (neat) 3400, 1715, 1490, 1450, 1380, 1200, 1105, 1025, 1000, 910, 745, 700; ^1H NMR (200 MHz, $CDCl_3$) 0.83 (t, 3 H, J = 7.6 Hz, CH_2CH_3), 1.01 (s, 3 H, CH_3), 1.1–1.8 (m, 2 H, CH_2CH_3), 4.95 (s, 1 H, CHOH), 7.32 (s, 5 H, C_6H_5), 9.70 (s, 1 H, CHO).

The aldolates **7c** and **8c** slowly decompose at room temperature. Therefore, they are fully characterized after silylation by chlorotrimethylsilane and triethylamine in the presence of catalytic amount of 4-(dimethylamino)pyridine in THF.

Duplication of the reaction using 0.792 g of **4** (5.0 mmol), 2.65 g of benzaldehyde (25 mmol), and 0.71 g of BF_3·OEt_2 (5.0 mmol) afforded the silylated aldol products in 43% yield (556 mg, 2.1 mmol).

(2*RS*,1′*RS*)-1-(((Trimethylsiloxy)phenyl)methyl)-2-methyl-1-butenal: IR (neat) 1710, 1440, 1240, 1110, 1080, 1060, 1020, 865, 830, 735, 685; ^1H NMR (200 MHz, $CDCl_3$) −0.03 (s, 9 H, $Si(CH_3)_3$), 0.78 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 0.98 (s, 3 H, CH_3), 1.0–2.0 (m, 2 H, CH_2CH_3), 4.71 (s, 1 H, CHOSiMe$_3$), 7.1–7.7 (m, 5 H, C_6H_5), 9.67 (s, 1 H, CHO). Anal. ($C_{15}H_{24}O_2Si$): C, H.

(2*RS*,1′*SR*)-1-(((Trimethylsiloxy)phenyl)methyl)-2-methyl-1-butenal: IR (neat) 1710, 1440, 1350, 1240, 1080, 1060, 860, 830, 735, 690; ^1H NMR (200 MHz, $CDCl_3$) −0.05 (s, 9 H, $Si(CH_3)_3$), 0.74 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 0.92 (s, 3 H, CH_3), 1.1–2.0 (m, 2 H, CH_2CH_3), 4.77 (s, 1 H, CHOSiMe$_3$), 7.26 (m, 5 H, C_6H_5), 9.65 (s, 1 H, CHO). Anal. ($C_{15}H_{24}O_2Si$): C, H.

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Supplementary Material Available: Details of the chemical transformation carried out for the structure determination of the aldols (7 pages). Ordering information is given on any current masthead pages.