3.41-3.55 (m, 1 H), 3.39 (s, 3 H), 3.32 (s, 3 H), 3.29-3.40 (m, 2 H), 2.23-2.46 (m, 2 H), 1.48-1.92 (m, 5 H), 1.13-1.41 ppm (m, 2 H); mass spectrum, exact mass (M^+) calcd 230.1518, found 230.1530.

3-Oxa-2,7-dimethoxy-8-carbomethoxy-*cis*-decalin (17). The primary alcohol **16c** was oxidized exactly according to the procedure of Swern[22] to provide the corresponding aldehyde in 84.5% yield as an oil: IR (CCl_4) 1726 cm^{-1} (s); ^1H NMR 9.74 (d, J = 2.0 Hz, 1 H), 4.64 (br dd, 1 H), 3.94-4.01 (dd, 1 H), 3.61-3.74 (td, 1 H), 3.38 (s, 3 H), 3.32 (s, 3 H), 3.15-3.40 (m, 1 H), 2.69-2.84 (m, 1 H), 2.27-2.44 (m, 2 H), 1.39-1.99 (m, 5 H), 1.10-1.31 ppm (m, 1 H); mass spectrum, exact mass ($M^+ - CH_3$) calcd 213.1127, found 213.1130.

To a solution of the aldehyde (89.1 mg, 0.4 mmol) and acetone cyanohydrin (71.4 μL, 2 equiv) in CH_2Cl_2 was added triethylamine (10 μL, 0.2 equiv) and the solution stirred under nitrogen overnight. Solvent was removed in vacuo, leaving a white solid (the cyanohydrin of the starting aldehyde). The cyanohydrin was used in this crude form and displayed no aldehydic proton in the ^1H NMR and was diastereomeric at the newly generated chiral center: IR (CCl_4) 3450 cm^{-1} (m); mass spectrum, m/e 224 ($M^+ - OCH_3$).

In a separate flask, oxalyl chloride (44 μL, 1.2 equiv was dissolved in CH_2Cl_2 (1.1 mL) and chilled to -78 °C and Me_2SO (110 μL, 4 equiv) added dropwise. After 15 min, a solution of the aldehyde cyanohydrin prepared as described above in CH_2Cl_2 was added. The solution was stirred at -78 °C for 30 min and at -25 °C for 30 min and chilled back to -78 °C and NEt_3 (271 μL, 5 equiv) added. After being stirred at -78 °C for 10 min, the mixture was warmed to -25 °C for 15 min and quenched with methanol (0.6 mL). After a gradual warming to room temperature, the solution was stirred overnight, poured onto water, and extracted with $CHCl_3$ (3×, 25 mL total), and the extracts were combined, washed with water, dried (Na_2SO_4), filtered, concentrated, and chromatographed on silica with 20:80 ethyl acetate-hexane to afford the methyl ester as a white solid in 65.0% yield: IR (CCl_4) 1737 cm^{-1} (s); ^1H NMR 4.66 (d, J = 1.3 Hz, 1 H), 3.88-3.95 (dd, 1 H), 3.68 (s, 3 H), 3.45-3.60 (m, 1 H), 3.35 (s, 3 H), 3.31 (s, 3 H), 3.30-3.36 (m, 1 H), 2.46-2.67 (m, 2 H), 2.20-2.32 (m, 1 H), 1.71-1.96 (qd, 2 H), 1.47-1.62 (m, 2 H), 1.34-1.44 (dd, 1 H), 1.07-1.27 ppm (m, 1 H); mass spectrum, exact mass (M^+) calcd 258.1467, found 258.1475.

3-Oxa-2-hydroxy-7-methoxy-8-carbomethoxy-*cis*-decalin (18). A solution of 2-methoxy-3-oxadecalin **17** (18.2 mg) in THF (1 mL) and aqeuous 1 N HCl (1 mL) was stirred at room temperature for 21 h, poured onto brine (4 mL), and extracted with ethyl ether (3×, 25 mL total), the ether combined, washed with water, dried ($MgSO_4$), filtered, and concentrated, and the clear oily residue (homogeneous by TLC) chromatographed on silica with 50:50 ethyl acetate-hexane to afford a clear oil: 13.0 mg (76.0%); IR (neat) 3400 (br m), 1732 cm^{-1} (s); ^1H NMR 5.28 (br s, 1 H), 4.52-4.61 (m, 1 H), 4.17-4.23 (m, 1 H), 3.79 (d, 1 H), 3.70 and 3.71 (each a s, combined integral = 6 H), 3.46-3.68 (m, 3 H), 3.35 (s, 6 H), 3.32-3.40 (m, 1 H), 2.49-2.71 (m, 4 H), 1.09-2.35 (m, 14 H) [note: each proton of one anomer counts as 1 H]; mass spectrum, exact mass ($M^+ - H_2O$) calcd 226.1205, found 226.1208.

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Acyclic Stereoselection. 36. Simple Diastereoselection in the Lewis Acid Mediated Reactions of Enol Silanes with Aldehydes[1]

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The Lewis acid mediated aldol reactions of enol silanes with aldehydes have been investigated. The effects of enol silane structure, both nature of the ligand at the silyloxy carbon and the geometry of the double bond, the aldehyde structure, and the nature of the Lewis acid have been studied. In general, the reactions of prochiral enol silanes with prochiral aldehydes show little simple diastereoselection (Table I). An exception is *Z* enol silane **7**, derived from ethyl *tert*-butyl ketone, which shows synthetically useful anti selectivity. Enol silane **36** may therefore be used as an anti-selective propionate equivalent. The chiral α-alkoxy aldehyde **43** shows a high diastereofacial preference in its reactions with enol silanes **42c** and **42d** provided a Lewis acid capable of expanding its coordination beyond four is used ($TiCl_4$ or $SnCl_4$) (Table II). However, with the related ketene acetal **41b**, only modest diastereofacial selectivity is seen (Table II). Aldehyde **43** also shows a high diastereofacial preference, in the chelation-controlled sense, in its reactions with prochiral enol silanes **5-9**. However, the simple diastereoselection observed in the latter reactions (Table III) is quite different from that observed in the reactions of prochiral aldehydes with the same enol silanes. For example, enol silane **7**, which shows good anti selectivity in its reactions with prochiral aldehydes, gives a 1.5:1 mixture of the two syn aldols in its reaction with **43**; while the reverse is true with the propiophenone-derived enol silanes **8** and **9**. Finally, the results obtained in this study, along with those reported by other investigators, have been formulated into a coherent mechanistic rationale involving open transition states of the sort depicted in Figures 1 and 3.

In the last ten years there has been a resurgence of interest in the aldol addition reaction,[3] particularly from the standpoint of its stereochemistry.[4] Most of the stereochemical investigations to date have dealt with the uncatalyzed reactions of preformed enolates, mainly lithium, boron, and zinc,[4] with aldehydes. Recently, several groups have turned their attention to the analogous Lewis

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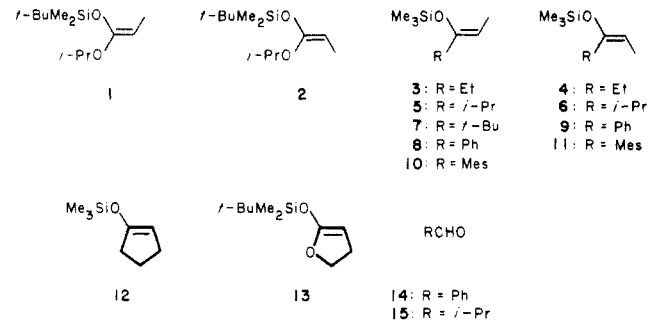
acid mediated process—reactions of enol silanes[5-14] and allylsilanes[9,15-20] with aldehydes. Similar studies have appeared pertaining to the trimethylsilyl triflate catalyzed reactions of enol silanes with aldehydes.[21] In this paper, we provide a full account of our investigations of simple diastereoselection and diastereofacial selection in the Lewis acid mediated reactions of enol silanes with aldehydes.

Simple Diastereoselection. The first question we addressed was the stereochemical outcome of the reactions of prochiral enol silanes with prochiral aldehydes (simple diastereoselection).[22] Enol silanes **1–13** and aldehydes **14–15** were employed in this study. The *Z* ketene acetal



1 was prepared by the treatment of isopropyl propionate with lithium diisopropylamide (LDA) in tetrahydrofuran (THF), followed by reaction of the resulting lithium enolate with *tert*-butyldimethylsilyl chloride. The corresponding *E* ketene acetal **2** (89% isomeric purity) was prepared by the method of Ireland.[23] Initial attempts to prepare the trimethylsilyl ketene acetals derived from ethyl, isopropyl, or *tert*-butyl propionate were complicated by the tendency of this silyl chloride to react on carbon, as well as on oxygen, to give inseparable separable mixtures of isomers. The pure *Z* enol silane **3** was prepared from 3-pentanone by the method of Kuwajima, Nakamura, and Hashimoto.[24] The isomeric *E* enol silane **4** was obtained by treatment of 3-pentanone with lithium 2,2,6,6-tetramethylpiperidide in THF, followed by trimethylsilyl chloride; under these conditions, *E* and *Z* enol silanes **4** and **3** are produced in a ratio of 86:14. The isomeric enol silanes from 2-methyl-3-pentanone (**5** and **6**) were obtained by successive treatment of the ketone with LDA and trimethylsilyl chloride in THF; the resulting mixture of *Z* and *E* isomers was separated by preparative high performance chromatography (HPLC). Enol silane **7** is produced in a state of high isomeric purity by the reaction of 2,2-dimethyl-3-pentanone with LDA in THF, followed by trimethylsilyl chloride. The *Z* enol silane from propiophenone, **8**, is obtained as the only isomer by treatment of the ketone with LDA and trimethylsilyl chloride in THF. If lithium bis(trimethylsilyl)amide is employed as base, *Z* and *E* isomers **8** and **9** are produced in a ratio of 70:30; the latter isomer was obtained in a pure state by preparative HPLC. Reaction of ethyl mesityl ketone with potassium bis(trimethylsilyl)amide in THF followed by trimethylsilyl chloride provides pure *Z* enol silane **10**. If the same ketone is used with LDA in ether, the *E* enol silane **11** is obtained in 93% isomeric purity.[25] The cyclic enol silanes **12** and **13** were prepared from cyclopentanone and γ-butyrolactone, respectively, by successive treatment with LDA and the appropriate silyl chloride in THF.

As Lewis acids we employed boron trifluoride etherate, titanium tetrachloride, and stannic chloride. All reactions were carried out in methylene chloride at −78 °C (eq 1–2). In some cases, the products consisted of a mixture of aldols and silylated aldols. In such cases, the product mixture was treated with *N*-(trimethylsilyl)imidazole prior to analysis. Aldol products were identified by comparison with previously known materials.[26]

Two practical aspects of the reactions summarized in eq 1 should be noted at this point. The first concerns the reactions involving isobutryaldehyde with boron trifluoride etherate as catalyst (Table I, entries 6, 10, 16). In a typical reaction, a solution of 1.0 mmol of aldehyde in 4.0 mL of methylene chloride is cooled to −78 °C and 1.0 mmol of Lewis acid is added in one portion; after 15 min, 1.2 mmol

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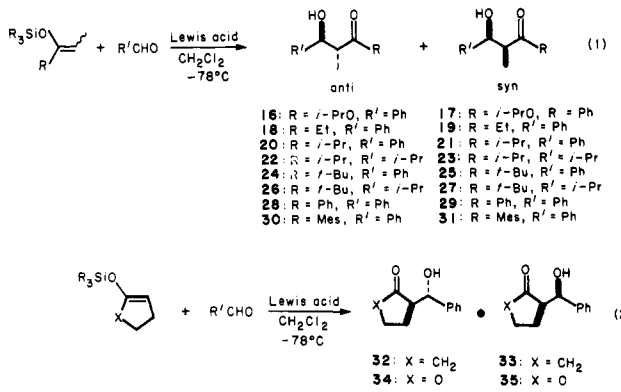
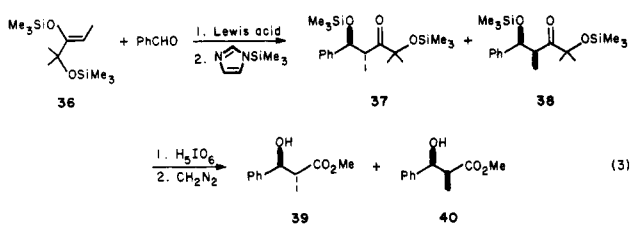


of enol silane is added by syringe over a 30-min period. If this procedure is used with isobutyraldehyde, the aldehyde is rapidly transformed into the cyclic trimer, 2,4,6-triisopropyl-1,3,5-trioxane.[27] This side reaction is totally eliminated by premixing the aldehyde and enol silane prior to addition of the Lewis acid.

The second problem we encountered was with the titanium tetrachloride mediated reactions of benzaldehyde and enol silane **7** (Table I, entry 15). Under the standard conditions (premixing the aldehyde and Lewis acid), benzaldehyde and titanium tetrachloride form a yellow precipitate which does not always disappear after addition of the enol silane. Consequently, this reaction is not reproducible. However, if the enol silane and aldehyde are premixed prior to addition of the Lewis acid the insoluble complex does not appear. Instead, the clear, colorles solution gradually assumes a red-brown color over a period of 15 min. Control experiments showed no difference in product yield or diastereomer ratio over a 4-h period at −78 °C when this protocol was followed. It is interesting that this problem did not arise with the same combination of reactants when stannic chloride was used as Lewis acid, or with titanium tetrachloride and other combinations of enol silane and aldehyde.

The data in Table I show that there is virtually no simple stereoselection in these reactions, in contrast to earlier reports.[6,28] The sole exception is the *Z* enol silane from ethyl *tert*-butyl ketone (**7**), which gives preparatively useful ratios of the anti diastereomers **24** and **26** (Table I, entries 13–18). In order to capitalize on this useful observation, we prepared the enol silane **36** from the known ketone[26,29] and examined its reactions with benzaldehyde. With boron trifluoride etherate as catalyst, anti and syn aldols **37** and **38** are produced in a ratio of 5:1; with titanium tetrachloride, the same two products are obtained in a ratio of 9:1 (eq 3). Cleavage with periodic acid, followed by diazomethane esterification, provides β-hydroxy esters **39** and **40**.



At this point, on the basis of the stereochemistry seen in the reactions summarized in Table I, we shall advance

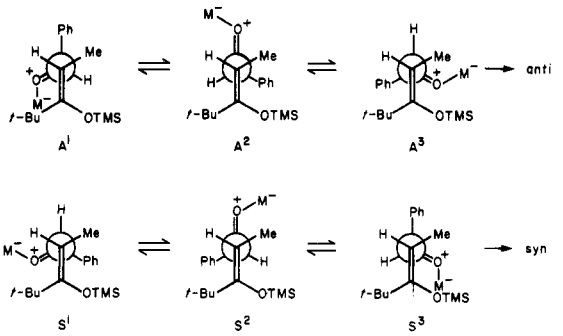


Figure 1. Staggered transition states for reaction of enol silane **7** with benzaldehyde.

a model for the mechanism of the Lewis acid mediated reactions of enol silanes with aldehydes. The staggered transition states for the Lewis acid mediated reaction of the *Z* enol silane from ethyl *tert*-butyl ketone with benzaldehyde are summarized in Figure 1. It is assumed that the Lewis acid occupies a coordination site on the carbonyl oxygen such that it is cis to the aldehyde hydrogen.[8a,9f] Transition states A^3 and S^3 are disfavored by the unfavorable dipole–dipole interaction of the two carbon–oxygen bonds. Arrangement A^3 is further destabilized by the nonbonded interaction between phenyl and *tert*-butyl, as is transition state S^2. The three remaining candidates are A^1, A^2, and S^1. We can probably rule out A^1 because of steric interaction between the *tert*-butyl and the Lewis acid, and we can eliminate S^1 since it contains *both* *tert*-butyl:oxygen and phenyl:OTMS nonbonded interactions. Thus, the reaction leads to the anti products **24** and **26**, perhaps by way of transition state A^2. If the *tert*-butyl group is replaced by a smaller group, it is expected that stereoselectivity would diminish, since more conformations (e.g., A^1, S^1, S^2) would become viable.

Note that we specifically exclude chelated transition states in this analysis, although such transition states have been advanced by others.[6,28] The corresponding lithium enolate, which almost certainly reacts by way of a six-centered, lithium-chelated transition state, gives solely syn aldols.[29,30] In contrast, enol silane **7** gives only anti products in its reactions. Furthermore, the three Lewis acids investigated, titanium tetrachloride, stannic chloride, and boron trifluoride, give essentially the same results in comparable cases (e.g., Table I, entries 6–8, 10–12, 13–15, 16–18). It is difficult to imagine a manner in which BF_3 could form a chelated structure. A recent INEPT ^{29}Si NMR study aimed at providing further insight into the titanium tetrachloride mediated reaction was inconclusive.[31] In a recent study of the $TiCl_4$-mediated reaction of bis-silyl ketene acetals with aldehydes[10b] Dubois and co-workers also concluded that "chelated six-membered ring transition states (for such reactions) are not totally adequate..." We believe that the Dubois results are in good agreement with the prediction made by the analysis given in Figure 1 in that the ketene acetal from propanoic acid gives mainly (6:1 to 8:1) the anti aldol (transition state A^2) while that from 3,3-dimethylbutanoic acid gives mainly (3:1 to 8:1) the syn aldol (transition state S^2).

Diastereofacial Selection. α-Alkoxy Aldehydes. For this phase of our investigation, we employed enol silanes **5–9**, **41a**, **41b**, **42c**, **42d**, and O-benzyllactaldehyde (**43**).[32] For the achiral ketene acetals **41a** and **41b**, little stereo-

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Table I. Diastereomer Ratios in the Reactions of Enol Silanes with Aldehydes (eq 1-2)

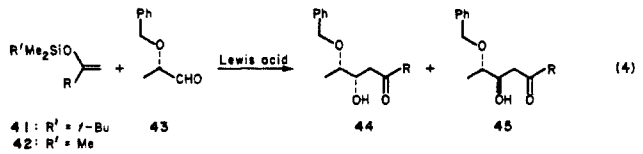
entry	enol silane	aldehyde	Z/E ratio	Lewis acid	yield, %	products anti, syn	isomer ratio, anti/syn[a]
1	**1**	**14**	100:0	$SnCl_4$	42	**16, 17**	63:37
2	**2**	**14**	11:89	$SnCl_4$	48	**16, 17**	70:30
3	**3**	**14**	100:0	$BF_3{\cdot}Et_2O$	62	**18, 19**	40:60
4	**4**	**14**	14:36	$BF_3{\cdot}Et_2O$	52	**18, 19**	43:57
5	**5**	**14**	97:3	$BF_3{\cdot}Et_2O$	57	**20, 21**	44:56
6	**5**	**15**	97:3	$BF_3{\cdot}Et_2O$	83	**22, 23**	44:56[b,c]
7	**5**	**15**	97:3	$SnCl_4$	70	**22, 23**	45:55[c]
8	**5**	**15**	97:3	$TiCl_4$	68	**22, 23**	54:46[c]
9	**6**	**14**	0:100	$BF_3{\cdot}Et_2O$	71	**20, 21**	65:35
10	**6**	**15**	0:100	$BF_3{\cdot}Et_2O$	77	**22, 23**	30:70[b,c]
11	**6**	**15**	0:100	$SnCl_4$	81	**22, 23**	42:58[c]
12	**6**	**15**	0:100	$TiCl_4$	73	**22, 23**	34:66[c]
13	**7**	**14**	100:0	$BF_3{\cdot}Et_2O$	95	**24, 25**	>95:5
14	**7**	**14**	100:0	$SnCl_4$	72	**24, 25**	>95:5
15	**7**	**14**	100:0	$TiCl_4$	53	**24, 25**	>95:5[b]
16	**7**	**15**	100:0	$BF_3{\cdot}Et_2O$	84	**26, 27**	>95:5[b]
17	**7**	**15**	100:0	$SnCl_4$	60	**26, 27**	>95:5
18	**7**	**15**	100:0	$TiCl_4$	65	**26, 27**	>95:5
19	**8**	**14**	100:0	$BF_3{\cdot}Et_2O$	63	**28, 29**	53:47
20	**9**	**14**	0:100	$BF_3{\cdot}Et_2O$	52	**28, 29**	70:30
21	**10**	**14**	100:0	$SnCl_4$	62	**30, 31**	72:28
22	**11**	**14**	7:93	$SnCl_4$	70	**30, 31**	72:287
23	**12**	**14**	0:100	$BF_3{\cdot}Et_2O$	78	**32, 33**	60:40
24	**13**	**14**	0:100	$BF_3{\cdot}Et_2O$	82	**34, 325**	39:61

[a] Unless otherwise stated, ratios were determined by 250-MHz ^1H NMR and 62.9-MHz ^{13}C NMR. In several cases the crude reaction product was silylated with (trimethylsilyl)imidazole prior to analysis. [b] In this case, the aldehyde and enol silane were premixed before addition of the Lewis acid at −78 °C. [c] Ratios were determined by capillary GC.

Table II. Diastereomer Ratios in the Reactions of Achiral Enol Silanes with Aldehyde 43 (eq 4)

entry	enol silane	Lewis acid	yield, %	products	isomer ratio, anti/syn
1	**41a**	$BF_3{\cdot}Et_2O$	48	**44a, 45b**	60:40
2	**41b**	$SnCl_4$	65	**44b, 45b**	65:35
3	**42c**	$SnCl_4$	86	**44c, 45c**	>99:1
4	**42d**	$SnCl_4$	68	**44d, 45d**	>99:1
5	**42d**	$TiCl_4$	70	**44d, 45d**	>99:1

selectivity is observed, either with boron trifluoride etherate or with stannic chloride (eq 4, Table II, entries 1 and 2). However, the achiral enol silanes **42c** and **42d** give only a single product (**44c**, **44d**) with stannic chloride or titanium chloride as catalyst (eq 4, Table II, entries 3–5).



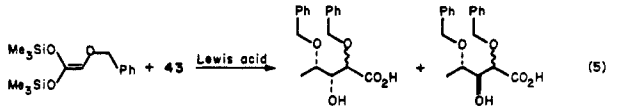
41: R' = *t*-Bu **42**: R' = Me **43** **44** **45**

a: R = MeO, b: R = *t*-BuO, c: R = *t*-Bu, d: R = Ph

Because of the high stereoselectivity observed with enol silanes **42c** and **42d**, it is assumed that **44c** and **44d** have the *R,R* relative stereochemistry, as shown. Subsequent rigorous assignments of related aldols add support to this assumption (vide infra). This relative configuration is that expected to result from addition of the nucleophile to the less encumbered face of the chelated α-alkoxy aldehyde (Figure 2).

Figure 2. Illustration of *lk* attack of an enol silane on a chelated α-alkoxy aldehyde.

The lack of facial selectivity in the boron trifluoride mediated reaction of ketene acetal **41a** with **43** (Table II, entry 1) is not surprising, as this Lewis acid is unlikely to expand its ligancy beyond four, and is therefore not expected to be chelated by the two oxygens of the substrate aldehyde. The low selectivity seen with ketene acetal **41b** and **43** is, however, unexpected. We do not have a solid rationale to advance for this behavior. However, it should be noted that the related ketene acetal **46** reacts with aldehyde **43** to give $C_{3,4}$-syn:$C_{3,4}$-anti ratios of 60:40 with BF_3-etherate, 72:28 with $SnCl_4$, and 66:34 with $TiCl_4$ (eq 5).[8d]



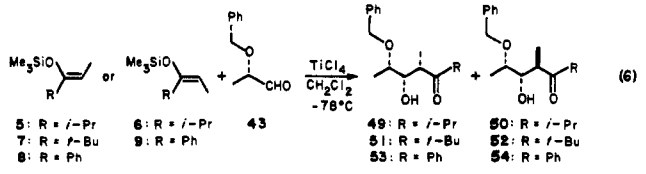
46 **47** **48**

The next reactions we investigated were those involving the prochiral enol silanes **5–9** with aldehyde **43**. In each case, only two of the four possible diastereomers were obtained (eq 6). Results are summarized in Table III.

Stereostructures were assigned to aldols **49–54** in the following manner. First, it is clear from spectral com-

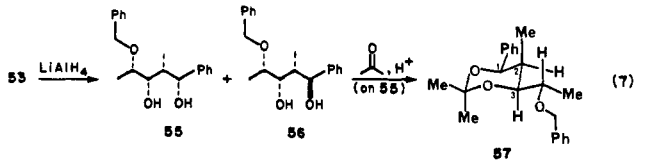
Table III. Diastereomer Ratios in the Reactions of Prochiral Enol Silanes with Aldehyde 43 (eq 6)

entry	enol silane	Z/E ratio	Lewis acid	yield, %	products	isomer ratio
1	**5**	100:0	$TiCl_4$	75	**49, 50**	50:50
2	**6**	0:100	$TiCl_4$	73	**49, 50**	88:12
3	**7**	100:0	$SnCl_4$	66	**51, 52**	59:41
4	**8**	100:0	$TiCl_4$	79	**53, 54**	95:5
5	**8**	100:0	$SnCl_4$	85	**53, 54**	95:5
6	**9**	0:100	$TiCl_4$	73	**53, 54**	85:15
7	**9**	0:100	$SnCl_4$	87	**53, 54**	75:25



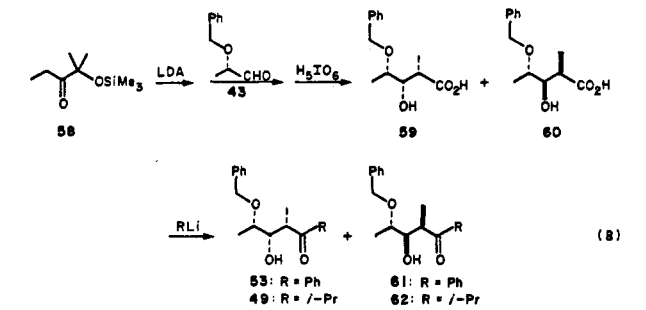
(6)

parison of the separated products that the *Z* and *E* propiophenone enol silanes (**8** and **9**) give the same two products (Table III, entries 4–7), in contrast to the report of Reetz and Kessler.[9d] The structure of **53**, the major isomer from both **8** and **9**, has been assigned by Reetz and co-workers on the basis of single-crystal X-ray analysis.[9b] We have provided independent verification of this assignment by lithium aluminum hydride reduction of the major aldol, which provides diastereomeric diols **55** and **56** in a ratio of 4:1. The major product of this reduction was converted into acetonide **57** (eq 7). The vicinal coupling constant of 2.2 Hz observed between the C-2 and C-3 protons in the ^{1}H NMR spectrum of **57** indicates an axial–equatorial arrangement of these two protons and corresponds to a C-2, C-3-syn configuration in aldol **53**.



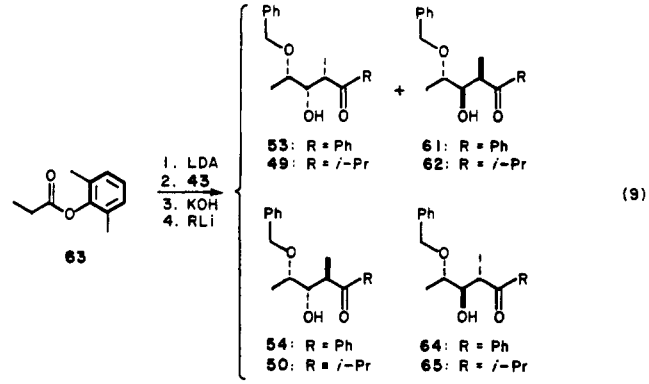
(7)

In order to assign a structure to the minor isomer, and to assure that we can distinguish the various isomers, we carried out independent syntheses of all four diastereomeric 4-(benzyloxy)-3-hydroxy-2-methyl-1-phenylpentan-1-ones. Addition of the lithium enolate of ketone **58**[26,33] to aldehyde **43** followed by periodic acid cleavage of the resulting product affords diastereomeric β-hydroxy acids **59** and **60** in a ratio of 30:70. The structures of **59** and **60** have been rigorously established by debenzylation and conversion of the resulting dihydroxy acids into the known γ-valerolactones.[32] Treatment of the mixture of **59** and **60** with excess phenyllithium gave a separable mixture of aldols **53** and **61** in a ratio of 30:70 (eq 8).



(8)

A mixture of all four aldols was produced by addition of the lithium enolate of 2,6-dimethylphenyl propionate (**63**)[34] to aldehyde **43**, saponification of the resulting mixture of β-hydroxy esters, and treatment of the hydroxy acids with excess phenyllithium (eq 9). From this sequence of reactions, aldols **53**, **54**, **61**, and **64** were obtained in a ratio of 13:26:29:32 and separated by preparative HPLC.[35] With all four possible aldols in hand, we were



(9)

able to confirm that the isomers can, in fact, be distinguished by both ^{1}H and ^{13}C NMR spectroscopy. Of these four materials, two (**61** and **53**) have been correlated with known compounds by way of the major and minor C-2, C-3-syn aldols from the reaction of the lithium enolate of **58** with aldehyde **43**. The structure of **53** is further secured by Reetz's X-ray analysis. The major product of reaction of the propiophenone enol silanes with aldehyde **43** is **53**. The minor isomer from these reactions is *not* **61**; therefore, this substance must be one of the C-2, C-3-anti aldols, **54** or **64**. Of these two possibilities, we have chosen **54**, because it is the expected product of chelation control.

A similar series of experiments was used to assign structures to the two aldols arising from reactions of the 2-methyl-3-pentanone enol silanes with aldehyde **43** (Table III, entries 1 and 2). Authentic samples of aldols **49** and **62** were obtained by reaction of hydroxy acids **59** and **60** with isopropyllithium (eq 8). A mixture of all four possible aldols was produced as shown in eq 9. As in the phenyl series, **49**, **50**, **62**, and **65** were separated for spectral characterization.

Examination of the data in Table III shows an interesting dichotomy. With the propiophenone enol silanes, the diastereofacial preference of aldehyde **43** is greater with the *Z* isomer than it is with the *E* isomer (cf. entries 4/6 and 5/7). However, with the 2-methyl-3-pentanone enol silanes, greater selectivity is seen with the *E* isomer (cf. entries 1/2). This apparently different behavior caused us to question the rigor of the stereostructural assignments of the isomeric enol silanes **5** and **6**. These isomers were among a collection of isomeric enol silanes examined first by House and co-workers,[36] who developed the rule of thumb that ^{1}H NMR resonance of a vinyl hydrogen cis to a silyloxy group is deshielded relative to one trans to a silyloxy group. However, the vinyl hydrogen resonances in **5** and **6** are almost the same (4.54 and 4.47 ppm, respectively), and the House method can therefore not be employed. We subsequently assigned structures to these enol silanes on the basis of the ^{13}C NMR shifts of the methine carbons, which differ by approximately 6 ppm.[26] In order to verify this assignment, nuclear Overhauser enhancement (NOE) experiments were carried out with **5** and **6**. Irradiation of the C(1)H_3 resonance of **5** resulted in NOE only of the C(2)H resonance, while irradiation of the C(1)H_3 resonance of **6** led to NOE of both the C(2)H and C(4)H signals. These results fully corraborate the earlier assignments based on ^{13}C NMR chemical shift.

(33) Young, S. D.; Buse, C. T.; Heathcock, C. H. *Org. Synth.* **1985**, *63*, 79.

(34) (a) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727. (b) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087. (c) Montgomery, S. H.; Pirrung, M. C.; Heathcock, C. H. *Org. Synth.* **1985**, *63*, 99.

(35) Reagent **63**, which shows high anti simple diastereoselection in its reactions with simple achiral aldehydes (ref 33), is often very *unselective* in its reactions with α-alkoxy aldehydes, as shown by the present example. While we have no ready explanation for this failing of **63**, we have noticed it on several occasions.

(36) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, M. D. *J. Org. Chem.* **1969**, *34*, 2324.

(37) Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451.

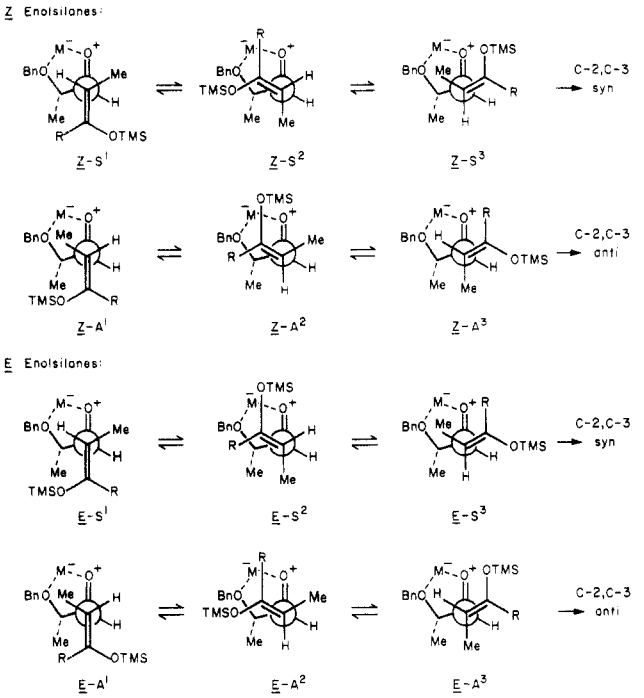


Figure 3. Staggered transition states for chelation-controlled, Lewis acid mediated reactions of prochiral enol silanes with 2-(benzyloxy)propanal.

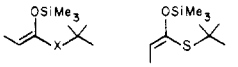
Reetz and co-workers have reported similar studies of the reactions of enol silanes **5**–**7**[9b,f] and of the *E* and *Z* enol silanes derived from 3-pentanone with aldehyde **43**.[9e] These workers obtained similar product ratios and also noted that with the 3-pentanone enol silanes the *Z* isomer leads to opposite simple diastereoselectivity compared to the *E* isomer.[9e] The only minor discrepancy between our results and those reported by the Reetz group concerns the identity of the minor product in the reaction of the *Z* propiophenone enol silane (**8**) with **43**, which was reported to be aldol **61** by Reetz, Kessler, and Jung[9f] and has been found to be aldol **54** in our study.

To rationalize the stereochemistry of the Lewis acid mediated reactions of prochiral enol silanes **5**–**9** with aldehyde **43** we refer to the Newman projections enumerated in Figure 3. The view in Figure 3 is along the forming bond, assuming that the six ligands on the two reacting carbons are staggered relative to one another. For both *Z* and *E* enol silanes, we disregard transition states S^2, S^3, A^1, and A^2 because of the steric interaction between the ligands on the chelated metal and R, Me, or TMSO. This leaves us with two competing transition states, S^1 and A^3, for both *Z* and *E* enol silanes.

For the *E* isomers the size of the R group should not effect stereoselectivity, since it interacts only with the aldehyde hydrogen in both S^1 and A^3. We propose that S^1 is favored over A^3 because of the unfavorable dipole–dipole interaction between the two C–O bonds, as has been previously discussed (vide supra). As a result, the *E* isomers are syn-selective and in about the same degree (Table III, entries 2, 6, 7).

For the *Z* isomers, however, the R group interacts with C-2 in transition state S^1 and with the metal ligands in transition state A^3. Thus, we can expect the syn:anti ratio to be related in some manner to the steric demand of R. It is difficult to make an a priori evaluation of the two transition states. In the case of enol silane **8**, the phenyl group probably prefers to maintain a coplanar relationship with the double bond. This would bring it into serious interaction with the metal ligands and thereby destabilize transition state *Z*-A^3. However, for more rotund R groups–*tert*-butyl and isopropyl, the interaction with C-2 of the aldehyde in transition state *Z*-S^1 may be comparable to the interaction with the metal ligands in *Z*-A^3. As a result, these two enol silanes are relatively unselective.

Gennari and co-workers have recently reported stannic chloride mediated additions of the *Z* and *E* trimethylsilylenol ethers formed from *tert*-butyl thiopropanoate (**67** and **66**) to aldehyde **43**.[12] [Note that these substances have the same relative configuration of **6** and **5**, respectively; the different stereochemical descriptors arise from the change of sequence rule priority associated with the sulfur atom.] In the Gennari et. al investigation, **67** gave the syn and anti chelation-controlled products (analogous to **49** and **50**) in a ratio of 85:15, while **66** gave the same two aldols in a ratio of 95:5. These results are easily incorporated into the current rationale. Note that the diastereomer ratio shown by **67** is almost exactly the same as is seen with **6** and **9**. With isomer **66**, we might expect the greater effective "length" of the *tert*-butylthio group to cause more interaction with the metal ligands than with C-2 of the aldehyde, thus destabilizing transition state *Z*-A^3 more than *Z*-S^1. As a result, **66** behaves in the same manner as **8**.



66: X = S **67**
68: X = O

In contrast to the high selectivity seen with the thio ketene acetal **66**, the analogous compound formed from *tert*-butyl propionate (**68**) is relatively unselective, giving the four aldols analogous to **53**, **54**, **61**, and **64** (see eq 9) in a ratio of 58:31:7:4 in its titanium tetrachloride mediated reaction with **43**.[9e] This observation is not inconsistent with our finding that ketene acetal **41b** shows less diastereofacial selectivity than enol silanes **42c** and **42d** in reactions with **43** (Table II). It is possible that the two oxygens of a ketene acetal undergo some kind of alternative association with stannic chloride or titanium tetrachloride, thus precluding the sort of chelation by the substrate that we have invoked in our discussions heretofore.

A final curious observation that might be related to the foregoing discussion is Reetz's finding that enol silane **36** undergoes stannic chloride mediated reaction with aldehyde **43** to give only a single product, that corresponding to structure **54**, even though the structurally related enol silane **7** gives two aldols in a ratio of about 1.5:1. It is possible that in this case also the second oxygen atom is involved in some sort of association with the Lewis acid, resulting in a transition state resembling *Z*-S^2 or *Z*-S^3 (see Figure 3).

In summary, our investigations have shown that Lewis acid mediated reactions of enol silanes generally show little simple diastereoselection except in special cases. With achiral aldehydes, enol silanes with a sterically demanding C-1 ligand such as *tert*-butyl (e.g., **7**) show synthetically useful anti stereoselection. This discovery allows conversion of ketone **58**, previously introduced as a syn-selective propionate equivalent,[26,29] to be used in the form of its enol silane **36** also as an anti-selective propionate equivalent. With chiral aldehydes, a different pattern of stereoselectivity is seen. Lewis acids that are capable of expanding their coordination number give high chelation control with most of the enol silanes investigated. In addition, a different pattern of simple diastereoselection is seen. For example, the propiophenone enol silanes **8** and **9**, which show little stereochemical preference in their reactions with achiral aldehydes, show high syn selectivity

in their reaction with chiral α-alkoxy aldehyde **43**. In contrast, enol silane **7**, which shows high anti selectivity in its reactions with achiral aldehydes, is unselective in its reaction with **43**. Finally, we have been able to put forth a coherent rationalization of the stereoselectivity seen in terms of the open transition states depicted in Figures 1 and 3.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All glassware was thoroughly dried in an oven and cooled in a desiccator. All manipulations involving air-sensitive materials were performed under nitrogen using Schlenk or vacuum line techniques, with air-sensitive materials being exposed only to thoroughly dried and degassed solvents. Ether and THF were distilled from sodium/benzophenone under nitrogen atmosphere immediately prior to use. Benzene, pentane, hexane, methylene chloride, pyridine, triethylamine, trimethylchlorosilane, titanium tetrachloride, stannic chloride, and boron trifluoride etherate were distilled from calcium hydride under a nitrogen atmosphere.

^{1}H NMR spectra were recorded with the UCB-200 (200 MHz), the UCB-250 (250 MHz), or the BVX-300 (300 MHz) Fourier transform NMR instruments at the University of California, Berkeley (UCB) NMR Facility and are reported in parts per million (δ) downfield from internal standard tetramethylsilane (Me_4Si). Significant ^{1}H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons and coupling constants in hertz. ^{13}C NMR spectra were recorded with the UCB-200 (50.78 MHz) or the BVX-300 (75.5 MHz) Fourier transform NMR spectrometers. All ^{13}C NMR spectra are proton decoupled and are reported in parts per million (δ) downfield from internal standard tetramethylsilane (Me_4Si). NMR spectra were recorded in $CDCl_3$ unless otherwise noted. Infrared spectra were recorded either as solutions in 0.1 mm NaCl cells or as neat films on NaCl plates with a Perkin-Elmer Model 283 spectrophotometer. Electron-impact and chemical ionization mass spectra were recorded at the UCB mass spectral facility with Atlas Ms-12, Consolidated 12-110B, or Finnegan 4000 mass spectrometers. Mass spectral data are recorded as m/z (intensity expressed as percent in total ion current). Gas–liquid partition chromatography (GLPC) was done with a Varian Aerography Model 920 gas chromatograph. Liquid chromatography was performed by using bench-top silica gel columns and high-pressure liquid chromatography was performed with a Waters Model ALC/GPC-244 liquid chromatograph (analytical) or a Water Prep LC/System 500 (preparative). Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California at Berkeley. Melting points were obtained on a Thomas/Hoover capillary melting point apparatus and are uncorrected.

Preparation of Enol Silanes 1–13, 41a, 41b, 42c, and 42d. Enol silanes were prepared by quenching the corresponding lithium enolate with trimethylchlorosilane or *tert*-butyldimethylchlorosilane. Representative procedures follow:

***Z* and [*E*] Silyl Ketene Acetal 1 and [2].** [Modifications in brackets refer to the *E* isomer **2**.] To a stirring solution of 6.7 mL of THF and 0.77 mL (5.5 mmol) of diisopropylamine at 0 °C was added 3.67 mL (5.5 mmol) of a 1.5 M solution of *n*-butyllithium in hexane. After 10 min, the solution was cooled to −78 °C and 5.00 mmol of ester [2.0 mL of hexamethylphosphoric triamide followed by 5.00 mmol of ester] was added over a 5-min period by syringe. After 2.5 min, a solution of 0.8270 g (5.50 mmol) of *tert*-butyldimethylsilyl chloride in 2.0 mL of hexamethylphosphoric triamide (HMPA) and 1.0 mL of hexane [0.8270 g (5.50 mmol) of *tert*-butyldimethylsilyl chloride in 1.6 mL of hexane] was added over a 30-sec period. The silyl ketene acetal solution was warmed to room temperature (30 min), diluted with 15 mL of ice-cold pentane, and washed quickly 3 times with ice cold water. The organic layer was then washed with saturated brine and dried over Na_2SO_4. The solvent was removed with a rotary evaporator and the resulting crude product was purified by distillation with a Kugelrohr apparatus (90 °C, 0.25 torr) to give a clear colorless liquid.

(*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropoxyprop-1-ene (1): ^{1}H NMR ($CDCl_3$) δ −0.02 (s, 6), 0.92 (s, 9), 1.19 (d, 6, J = 6.1), 1.50 (d, 3, J = 6.4), 3.48 (q, 1, J = 6.4), 4.10 (qq, 1, J = 6.1, 6.1); IR (film) 1683 cm^{-1}. [Lit.[37] ^{1}H NMR ($CDCl_3$) δ 1.48 (d, 3), 3.48 (q, 1), 4.12 (h, 1).]

(*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropoxyprop-1-ene (2): ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 6), 0.91 (s, 9), 1.18 (d, 6, J = 6.2), 1.47 (d, 3, J = 6.5), 3.78 (q, 1, J = 6.5), 4.32 (qq, 1, J = 6.2, 6.2); IR (film) 1687 cm^{-1}. [Lit.[37] ^{1}H NMR ($CDCl_3$) δ 1.46 (d, 3), 3.78 (q, 1), 4.34 (h, 1).]

(*Z*)-3-[(Trimethylsilyl)oxy]-2-pentene (3). This enol silane was prepared by the method of Kuwajima, Nakaemura, and Hashimoto:[24] ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 9), 1.00 (t, 3, J = 6), 1.50 (d, 3, J = 7), 2.01 (q, 2, J = 6), 4.51 (q, 1, J = 7); capillary GC 97.0% *Z*-isomer; IR (film) 2951, 1570, 1520 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 0.5, 10.6, 11.6, 29.5, 100.9, 152.6.

(*E*)-3-[(Trimethylsilyl)oxy]pent-2-ene (4). This enol silane was obtained as the major product of an 86:14 mixture of *E* and *Z* isomers by deprotonating diethyl ketone with lithium 2,2,6,6-tetramethylpiperidide, followed by treatment of the resulting enolate with trimethylsilyl chloride. The following spectral data were obtained from the foregoing mixture: ^{1}H NMR ($CDCl_3$) δ (*E* isomer) 0.15 (s, 9), 1.00 (t, 3, J = 6), 1.50 (d, 3, J = 7), 2.01 (q, 2, J = 6), 4.57 (q, 1 J = 7); ^{13}C NMR ($CDCl_3$) δ (*E* isomer) 0.1, 7.5, 11.3, 31.0, 100.0, 152.6.

(*Z*)- and (*E*)-3-[(Trimethylsilyl)oxy]-4-methyl-2-pentene (5 and 6). A solution of 2,2,6,6-tetramethylpiperidine (7.85 g, 9.38 mL, 55.6 mmol) in dry THF (50.0 mL) was placed into a 200-mL, three-necked, round-bottomed flask which was flushed with nitrogen and equipped with an alcohol thermometer and magnetic stirring bar. This solution was cooled to 0 °C, and *n*-butyllithium (32.9 mL of a 1.67 M solution in hexane, 55 mmol) was added slowly. After 10 min, the mixture was cooled to −70 °C and 2-methyl-3-pentanone (5.0 g, 50.0 mmol) was added dropwise over a 5-min period. The solution was stirred for 30 min, and trimethylsilyl chloride (7.0 mL, 6.0 g, 55.0 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The resulting solution was partitioned between pentane (50.0 mL) and saturated aqueous $NaHCO_3$ (50.0 mL). The pentane extract was separated, dried over $MgSO_4$, and concentrated with a rotary evaporator. The tetramethylpiperidine was removed from the crude product by flash chromatography on silica gel (70 g) with hexane/ethyl acetate (19:1) as the eluant to yield 7.0 g (81%) of a 65:35 (**5**:**6**) mixture as determined by integration of the methyl doublets at 0.93 and 1.01 ppm, respectively. The *E* and *Z* isomers were separated by preparative HPLC using two columns in succession and hexanes as eluant. The *E* isomer (**6**) eluted first (2.7 column volumes), followed by the *Z* isomer (**5**) (3.6 column volumes) and a small amount of the tetrasubstituted isomer (5.5 column volumes).

(*Z*)-3-[(Trimethylsilyl)oxy]-4-methyl-2-pentene (5): ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9), 1.02 (d, 6, J = 6.9), 1.51 (dd, J = 6.6, 1.2), 2.16 (septet, 1, J = 6.8), 4.54 (dq, 1, J = 6.6, 0.9); ^{13}C NMR ($CDCl_3$) δ 0.7, 10.9, 20.7, 34.4, 99.3, 156.7.

(*E*)-3-[(Trimethylsilyl)oxy]-4-methyl-2-pentene (6): ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9), 0.96 (d, 6, J = 6.8), 1.54 (d, 3, J = 6.9), 2.71 (septet, 1, J = 6.8), 4.48 (q, 1, J = 6.9); ^{13}C NMR ($CDCl_3$) δ 0.5, 11.3, 19.8, 28.0, 98.1, 156.4.

Nuclear Overhauser enhancement experiments were carried out with the pure enol silanes at 300 MHz. With each isomer the doublet for the vinyl methyl group (ca. 1.5 ppm) was irradiated. For isomer **5** enhancement was observed of the vinyl hydrogen signal only. For isomer **6** enhancement was observed of both the vinyl hydrogen and methine hydrogen signals.

(*Z*)-4,4-Dimethyl-3-[(trimethylsilyl)oxy]-2-pentene (7). Use of the general procedure with 7.03 g (62.0 mmol) of 2,2-dimethyl-3-pentanone gave 10.33 g (89%) of enol silane **7** as a colorless oil: bp 121–123 °C (90 torr); IR (film) 1665, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 9), 1.04 (s, 9), 1.52 (d, 3, J = 6.6), 4.60 (q, 1, J = 6.6).

(*Z*)-1-Phenyl-1-[(trimethylsilyl)oxy]-1-propene (8). Use of the general procedure with 16.6 mL (0.125 mol) of propiophenone gave 22.93 g (89%) of **8** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 9), 1.76 (d, 3, J = 6), 5.33 (q, 1, J = 6), 7.39 (m, 5); ^{13}C NMR ($CDCl_3$) δ 0.5, 11.6, 105.2, 125.2, 127.3, 128.0, 139.2, 149.9; IR (film) 3050, 2950, 1650 cm^{-1}.

(*E*)-1-Phenyl-1-[(trimethylsilyl)oxy]-1-propene (9). To a 50-mL, round-bottomed flask containing 10 mL of ether at 0 °C were added 1.20 mL (5.57 mmol) of hexamethyldisilazane (HMDS) and 3.57 mL (5.50 mmol) of 1.54 M *n*-butyllithium. The mixture was stirred for 10-min and then cooled to −78 °C. When the temperature had equilibrated, 0.640 mL (4.82 mmol) of propiophenone was added at a rate as to keep the temperature constant, and then 0.700 mL (5.53 mmol) trimethylsilyl chloride was introduced. The solution was allowed to warm to room temperature overnight, diluted with 10 mL of pentane, and washed with 0.5 N acetic acid, saturated aqueous $NaHCO_3$, distilled water, and brine. The organic layer was dried over $MgSO_4$, and the solvent was removed under aspirator vacuum to yield 0.64 g (65%) of **8** and **9** in a ratio of 5:2. Repeated attempts to distill the material (115 °C, 15 mm) resulted only in extensive foaming. Instead, the isomers were separated by preparative HPLC using two μ-Porasil columns in series and hexane as eluant; the *Z* isomer elutes first. Depending on the activity of the silica gel used, some recycling may be necessary in order to achieve best separation. In a normal run, approximately 0.07 g of pure *E* isomer was obtained (35% yield, based on the amount of *E* isomer in the mixture): ^1H NMR ($CDCl_3$) δ 0.13 (s, 9), 1.73 (d, 3, J = 7), 5.11 (q, 1, J = 7), 7.35 (m, 5); ^{13}C NMR ($CDCl_3$) δ 0.1, 13.0, 104.8, 127.4, 127.7, 128.3, 137.5, 149.6.

(*Z*)-1-(2,4,6-Trimethylphenyl)-1-[(trimethylsilyl)oxy]-1-propene (10).[25] Potassium hydride (1.20 g, 30.0 mmol, 48.9 g of a 24.6% oil dispersion) was added to a 250-mL round-bottomed flask equipped with a glass frit and ground glass joint (Schlenkware) and placed under a nitrogen atmosphere. The dispersion was stirred with hexane (25.0 mL) for 10 min and the solid potassium hydride was allowed to settle. The hexane extract was removed through the glass frit into an attached Erlenmeyer flask with the aid of a positive pressure of nitrogen. This washing procedure was performed 3 times. Dry THF (100 mL) and hexamethyldisilazane (6.00 mL, 27.8 mmol) were added and the solution was stirred at room temperature for 1.5 h. Slow evolution of hydrogen gas was noted. The reaction mixture was cooled to −78 °C and a solution of 2′,4′,6′-trimethylpropiophenone in THF (10.0 mL) was added over a period of 1 h with a syringe pump. The solution was stirred for an additional hour and reaction was quenched with trimethylchlorosilane. The cooling bath was allowed to warm to room temperature overnight and the reaction mixture was then partitioned between 25.0 mL each of pentane and saturated $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, and concentrated with a rotary evaporator. The residue was distilled through a short-path still under vacuum to obtain 5.43 g (87%) of enol silane **10** as a colorless liquid, bp 61–63 °C (0.45–0.55 torr). The material so prepared was shown by ^1H NMR spectroscopy to be a mixture of enol silane **10** (89%) and starting ketone (11%): ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H), 1.68 (d, 3, J = 6.6), 2.15 (br s, 9), 4.45 (q, 1, J = 6.6), 6.72 (br s, 2); IR (film) 2950, 1665, 1310, 1250 cm^{-1}.

(*E*)-1-(2,4,6-Trimethylphenyl)-1-[(trimethylsilyl)oxy]-1-propene (11).[25] A solution of diisopropylamine (7.7 mL, 5.56 g, 56 mmol) in dry ether (50.0 mL) was added to a 250-mL, three-necked, round-botomed flask which was flushed with nitrogen and equipped with an alcohol thermometer and magnetic stirring bar. This solution was cooled to 0 °C, and *n*-butyllithium (35.2 mL of 1.56 M solution in hexane, 55 mmol) was added slowly. After 10 min, the mixture was cooled to −70 °C with a dry ice/acetone bath, and 2′,4′,6′-trimethylpropiophenone (8.88 g, 50 mmol) was added, dropwise, over a 10-min period. The solution was stirred for 30 min, and trimethylsilyl chloride (7.0 mL, 6.00 g, 55 mmol) was added. The reaction mixture was warmed to room temperature over a 30-min period and stirred overnight. The resulting solution was partitioned between pentane (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The pentane extract was separated, dried over Na_2SO_4, and concentrated with a rotary evaporator to afford a yellow liquid. The crude product was distilled through a short-path distillation apparatus under reduced pressure to afford 10.7 g (86%) of a colorless liquid, bp 65–67 °C (0.50–0.65 torr), which was a 92:8 mixture of *E* and *Z* enol silanes as determined by analytical HPLC using a μ-Porasil column and hexane as eluant: IR (film) 2950, 1660, 1260, 1220, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (s, 9), 1.28 (d, 3 J = 6.6 Hz), 2.15 (br s, 9), 4.95 (q, 1, J = 6.6 Hz), 6.72 (br s, 2).

1-[(Trimethylsilyl)oxy]cyclopentene (12). Use of the general procedure with 1.33 mL (15.0 mmol) of cyclopentanone gave 1.69 g (72%) of pure enol silane **12**: bp 156–158 °C; IR (film) 1650, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 9), 1.80 (m, 2), 2.20 (m, 4), 4.60 (m, 1).

2-[(*tert*-Butyldimethysilyl)oxy]-4,5-dihydrofuran (13). Use of the general procedure with 3.84 mL (50.0 mmol) of γ-butyrolactone gave 4.2701 g (43%) of a colorless product: bp 51–54 °C (0.8 torr); IR (film) 1675, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.20 (s, 6), 0.93 (s, 9), 2.62 (td, 2, J = 9, 1), 3.69 (t, 1 J = 1), 4.30 (t, 2, J = 9). Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06. Found: C, 59.50; H, 10.34.

1-[(*tert*-Butyldimethylsilyl)oxy]-1-methoxyethene (41a). Use of the general procedure with 2.80 mL (0.035 mol) of methyl acetate gave 1.21 g (61%) of ketene acetal **41a** as a colorless oil, bp 36–39 °C (1 torr); IR (film) 1650, 1270, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.18 (s, 6), 0.92 (s, 9), 3.20 (m, 2), 3.56 (s, 3).

1-*tert*-Butoxy-1-[(*tert*-butyldimethylsilyl)oxy]ethene (41b). Use of the general procedure with 1.74 g (0.015 mmol) of *tert*-butyl acetate gave 2.11 g (61%) of the ketene acetal: bp 36–39 °C (1.0 torr); IR (film) 1650, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.11 (s, 6), 0.93 (s, 9), 1.29 (s, 9), 3.30 (d, 1, J = 1), 3.37 (d, 1, J = 1).

2-[(Trimethylsilyl)oxy]-3,3-dimethyl-1-butene (42c). A solution of lithium diisopropylamide in 50 mL of THF was prepared in the usual way from 7.00 mL (49.0 mmol) of diisopropylamine and 32.0 mL of a 1.5 M solution of *n*-butyllithium in hexane. To this solution was added 6.00 mL (48.0 mmol) of 3,3-dimethyl-2-butanone dropwise over a 15-min period. The resulting solution was allowed to stand at −78 °C for 20 min, 7.00 mL (55 mmol) of trimethylsilyl chloride was added in one portion, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was poured into 100 mL of pentane in a separatory funnel and washed with 50 mL of saturated aqueous $NaHCO_3$ and 100 mL of water, the layers were separated, and the pentane layer was dried ($MgSO_4$). The solvent was removed with a rotary evaporator and the crude material thus obtained was distilled through a short-path still to afford 6.07 g (73%) of the purified product: bp 95–97 °C (90 torr); IR (film) 1660, 1620, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 9), 0.90 (s, 9), 3.81 (d, 1, J = 1), 3.91 (d, 1 J = 1).

1-Phenyl-1-[(trimethylsilyl)oxy]ethylene (42d). To a dry, three-necked, 300-mL, round-bottomed flask equipped with a magnetic stirring bar, alcohol thermometer, and a rubber septum was added 6.67 mL (47.1 mmol) of diisopropylamine and 125 mL of THF. The solution was cooled to 0 °C and 30.6 mL (47.1 mmol) of a 1.54 M solution of *n*-butyllithium in hexanes was added dropwise over a 10-min period. The resulting yellow solution was stirred for 10 min and cooled to −70 °C, and 5.00 mL (42.9 mmol) of acetophenone was added over a 5-min period. The solution was stirred an additional 20 min and 5.97 mL (47.1 mmol) of freshly distilled chlorotrimethylsilane was added. The solution was stirred for a further 5 min and warmed to room temperature. The reaction mixture was transferred to a separatory funnel, diluted with ice-cold pentane, and washed rapidly with the following ice-cold solutions: (1) 0.5 N aqueous acetic acid, (2) saturated aqueous $NaHCO_3$, (3) distilled water, and (4) brine. The organic layer was dried over $MgSO_4$ and the solvents were removed with a rotary evaporator. The crude product was purified by flash chromatraphy using 50:1 hexane/ethyl acetate to give 4.68 g (57%) of **42d** as a light yellow oil: ^1H NMR ($CDCl_3$) δ 0.29 (s, 9), 4.45 (d, 1 J = 1.4), 4.93 (d, 1, J = 1.4), 7.35 (m, 3), 7.63 (m, 2). [Lit.[36] ^1H NMR (CCl_4) δ 4.27 (d, J = 1.7), 4.73 (d, J = 1.7), 7.05 (m, 3), 7.34 (m, 2).]

2-(Benzyloxy)propanal (43). This aldehyde was used both in the racemic form[32b] and as the *S* enantiomer.[8d,32a]

General Procedure for the Reaction of Enol Silanes and Silyl Ketene Acetals with Aldehydes 14, 15, and [43]. The following procedures were used for the reactions of enol silanes and silyl ketene acetals with achiral aldehydes **14** and **15**. [Certain modifications used with aldehyde **43** are inserted in brackets.]

Procedure A. To a stirring solution of 1.00 mmol of aldehyde and 4 mL of CH_2Cl_2 at −78 °C was added dropwise 1.00 mmol of distilled Lewis acid. The complex was stirred for 15 min [3 min] and 1.20 mmol of enol silane or silyl ketene acetal was added by syringe over a 30-min period [all at once]. After 4 h [5–15 min], reaction was quenched by rapidly injecting 2.5 mL of saturated

aqueous $NaHCO_3$. The mixture was warmed to room temperature and the aqueous layer was separated and extracted with two 30-mL portions of ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed with a rotary evaporator. The crude product was examined by ^1H NMR to determine the ratio of isomers. The pure aldol adducts were isolated by gravity chromatography on silica gel [by HPLC using a μ-Porasil column].

In some cases, the ^1H NMR spectrum of the crude product revealed it to be a mixture of β-hydroxy and β-silyloxy ketones. In these situations, the crude product was silylated (using *N*-(trimethylsilyl)imidazole in CH_2Cl_2) for ^1H NMR analysis of diastereomer ratios. To insure that the anti and syn assignments for these silylated isomers were correct, the crude mixture was separated and the individual isomers desilylated (tetra-*n*-butylammonium fluoride in THF) and characterized. Analytical data are given only for the desilylated products.

Procedure B. This modification of procedure A was used for several entries in Table I. To a stirring solution of 1.00 mmol of aldehyde, 1.20 mmol of enol silane, and 4 mL of CH_2Cl_2 at −78 °C was added dropwise 1.00 mmol of distilled Lewis acid. The solution was stirred for 4 h and then quenched by rapid addition of 2.5 mL of saturated aqeuous $NaHCO_3$. The mixture was warmed to room temperature and the aqueous layer was separated and extracted with two 30-mL portions of ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed with a rotary evaporator. The crude products were examined by ^1H NMR to determine the isomer ratio, and the pure aldols were then isolated by gravity chromatography on silica gel.

Isopropyl (2*SR*,3*RS*)-2-methyl-3-hydroxy-3-phenylpropionate (16) (anti isomer): ^1H NMR ($CDCl_3$) δ 0.99 (d, 3, J = 7.2), 1.18 (d, 3, J = 6.3), 1.23 (d, 3, J = 4.8), 2.74 (dq, 1 , J = 7.4, 7.2), 3.18 (d, 1, J = 4.3), 4.70 (dd, 1, J = 4.3, 7.4), 5.02 (qq, 1, J = 6.3, 4.8), 7.31 (br s, 5); ^{13}C NMR ($CDCl_3$) δ 14.5, 21.7, 31.6, 47.2, 68.1, 126.6, 127.9, 128.4, 141.7, 175.4; IR (film) 3480, 1722 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.23; H, 8.16. Found: C, 69.99; H, 8.14.

Isopropyl (2*SR*,3*SR*)-2-methyl-3-hydroxy-3-phenylpropionate (17) (syn isomer): ^1H NMR ($CDCl_3$) δ 1.10 (d, 3, J = 7.1), 1.13 (d, 3, J = 6.2), 1.18 (d, 3, J = 6.2), 2.71 (dq, 1, J = 7.1, 4.4), 3.01 (d, 1, J = 3.0), 4.97 (qq, 1, J = 6.2, 6.2), 5.03 (dd, 1, J = 4.4, 3.0), 7.28 (m, 5); ^{13}C NMR ($CDCl_3$) δ 11.0, 21.6, 46.5, 68.1, 73.7, 126.1, 127.4, 128.2, 141.4, 175.4; IR (film) 3485, 1720 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.23; H, 8.16. Found, C, 70.09; H, 8.13.

(1*SR*,2*RS*)-1-Hydroxy-2-methyl-1-phenylpentan-3-one (18) (anti isomer): ^1H NMR ($CDCl_3$) δ 0.89 (d, 3, J = 7), 1.00 (t, 3, J = 7), 2.20–2.62 (m, 2), 2.75–2.96 (m, 1), 2.99 (s, 1), 4.72 (dd, J = 8.2, 3.4), 7.30 (s, 5); IR (film) 3460 (br), 1710 cm^{-1}.

(1*SR*,2*SR*)-1-Hydroxy-2-methyl-1-phenylpentan-3-one (19) (syn isomer): ^1H NMR ($CDCl_3$) δ 0.96 (t, 3, J = 7), 1.05 (d, 3, J = 7), 2.20–2.62 (m, 2), 2.75–2.96 (m, 1), 3.21 (s, 1), 5.01 (d, 1, J = 3.6), 7.32 (s, 5); IR (film) 3460 (br), 1710 cm^{-1}.

(1*SR*,2*RS*)-1-Hydroxy-2,4-dimethyl-1-phenylpentan-3-one (20) (anti isomer): ^1H NMR ($CDCl_3$) δ 0.78–1.12 (m, 9), 2.62 (septet, 1, J = 7), 3.05 (dq, 1, J = 7, 7), 4.10 (br s, 1), 4.71 (d, 1, J = 7), 7.29 (br s, 5); IR (film) 3460, 1710 cm^{-1}.

(1*SR*,2*SR*)-1-Hydroxy-2,4-dimethyl-1-phenylpentan-3-one (21) (syn isomer): ^1H NMR ($CDCl_3$) δ 0.78–1.12 (m, 9), 2.50 (septet, 1, J = 7), 2.95 (dq, 1, J = 7.4), 4.1 (br s, 1), 4.91 (d, 1, J = 4), 7.29 (br s, 5); IR (film) 3460 (br), 1710 cm^{-1}.

(4*RS*,5*RS*)-5-Hydroxy-2,4,6-trimethylheptan-3-one (22) (anti isomer): ^1H NMR ($CDCl_3$) δ 0.85 (d, 3, J = 6.4), 0.88 (d, 3, J = 6.5), 1.00 (d, 3, J = 7.6), 1.12 (d, 6, J = 6.8), 1.67 (m, 1), 2.61 (br s, 1), 2.69 (m, 1), 2.86 (dq, 1, J = 6.9, 7.6), 3.38 (m, 1).

(4*RS*,5*SR*)-5-Hydroxy-2,4,6-trimethylheptan-3-one (23) (syn isomer): ^1H NMR ($CDCl_3$) δ 0.83 (d, 3, J = 6.5), 0.97 (d, 3, J = 5.4), 1.00 (d, 3, J = 7.6), 1.12 (d, 6, J = 6.8), 1.68 (m, 1), 2.75 (m, 1), 2.89 (dq, 1, J = 2.7, 7.7), 3.0 (d, 1, J = 2.5), 3.43 (m, 1).

(1*SR*,2*RS*)-1-Hydroxy-2,4,4-trimethyl-1-phenylpentan-3-one (24) (anti isomer): ^1H NMR ($CDCl_3$) δ 0.95 (d, 3, J = 7), 1.02 (s, 9), 3.27 (m, 1), 4.72 (d, 1, J = 7), 7.30 (br s, 5).

(4*RS*,5*RS*)-5-Hydroxy-2,2,4,6-tetramethylheptan-3-one (26) (anti isomer): ^1H NMR ($CDCl_3$) δ 0.89 (d, 3, J = 6.7), 0.94 (d, 3, J = 6.8), 1.05 (d, 3, J = 6.9), 1.15 (s, 9), 1.67 (m, 1), 2.32 (d, 1, J = 6.7), 3.18 (dq, 1, J = 7.0, 6.9), 3.48 (ddd, 1, J = 7.0, 6.7, 5.4); ^{13}C NMR ($CDCl_3$) δ 15.4, 15.9, 20.1, 26.3, 29.9, 42.3, 44.9, 78.8, 221.4; IR (CCl_4), 3600, 3500, 1705 cm^{-1}. [Lit.[38] ^1H NMR (CCl_4) δ 3.48 (d, 1, J = 8.1).]

(2*SR*,3*SR*)-2-Methyl-1,3-diphenyl-3-hydroxypropan-1-one (28) (anti isomer): ^1H NMR ($CDCl_3$) δ 1.03 (d, 3, J = 7), 3.76 (m, 1), 4.97 (d, 1, J = 8), 7.23–8.10 (m, 10).

(2*SR*,3*RS*)-2-Methyl-1,3-diphenyl-3-hydroxypropan-1-one (29) (syn isomer): ^1H NMR ($CDCl_3$) δ 1.17 (d, 3, J = 8), 3.76 (m, 1), 5.20 (d, 1, J = 4), 7.23–8.10 (m, 10).

(2*SR*,3*SR*)-2-Methyl-1-(2,4,6-trimethylphenyl)-3-phenyl-3-hydroxypropan-1-one (30) (anti isomer): ^1H NMR ($CDCl_3$) δ 1.30 (d, 3, J = 7), 2.21 (s, 9), 3.70 (m, 1), 5.00 (d, 1, J = 9), 6.82 (br s, 2), 7.50 (m, 5).

(2*SR*,3*RS*)-2-Methyl-(2,4,6-trimethylphenyl)-3-phenyl-3-hydroxypropan-1-one (31) (syn isomer): ^1H NMR ($CDCl_3$) δ 1.35 (d, 3, J = 6), 2.26 (s, 9), 3.70 (m, 1), 5.03 (d, 1, J = 5), 6.82 (br s, 2), 7.50 (m, 5).

(2*RS*,1′*SR*)-2-(Hydroxyphenylmethyl)cyclopentanone (32) (anti isomer): IR (film) 3500, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–2.6 (m, 7), 4.70 (d, 1, J = 9.1), 7.2–7.4 (m, 5).

(2*RS*,1′*RS*)-2-(Hydroxyphenylmethyl)cyclopentanone (33) (syn isomer): IR (film) 3500, 1735 cm^{-1}; ^1H NMR ($CDCl_3$: δ 1.4–2.6 (m, 7), 5.28 (d, 1, J = 2.6), 7.2–7.4 (m, 5).

(2*RS*,1′*SR*)-3-(Hydroxyphenylmethyl)dihydro-1(2*H*)-furanone (34) (anti isomer): colorless oil; IR (film) 3450, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.94 (m, 2), 2.90 (m, 1), 4.20 (m, 2), 4.39 (s, 1), 4.81 (d, 1, J = 8.7), 7.2–7.4 (m, 5).

(2*RS*,1′*RS*)-3-(Hydroxyphenylmethyl)dihydro-1(2*H*)-furanone (35) (syn isomer): white crystals, mp 110–111 °C; IR ($CHCl_3$) 3450, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (m, 1), 2.40 (m, 1), 2.90 (m, 1), 3.11 (s, 1), 4.15 (m, 1), 4.32 (m, 1), 5.36 (d, 1, J = 2), 7.2–7.4 (m, 5). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.57; H, 6.30.

(*Z*)-3,4-Bis[(trimethylsilyl)oxy]-4-methylpent-2-ene (36). To a solution of 4.0 mL (28.5 mmol) of diisopropylamine in 50 mL of THF at 0 °C was added 17.9 mL of a 1.40 M solution of *n*-butyllithium in hexane. The resulting solution was stirred for 15 min and cooled to −78 °C, and 4.71 g (25.0 mmol) of 2-methyl-2-(trimethylsilyloxy)pentan-3-one[33] was added over a 5-min period. After 30 min, 3.81 mL (30.0 mmol) of trimethylsilyl chloride was added and the reaction mixture was allowed to warm to room temperature. After 3 h at room temperature 25 mL of saturated aqueous $NaHCO_3$ was added. The resulting mixture was extracted with two 50-mL portions of pentane and the combined pentane layers were washed with one 20-mL portion of ice-cold 0.5 M acetic acid and one 50-mL portion of saturated aqueous $NaHCO_3$. The pentane solution was dried ($MgSO_4$) and the solvent was removed with a rotary evaporator to afford a crude, oily product. This material was purified by distillation with a short-path still to afford 4.96 g (76%) of colorless **36**: bp 58–62 °C (1.4 torr); IR (film) 1670, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 9), 0.20 (s, 9), 1.32 (s, 6), 1.50 (d, 3, J = 6.6), 4.85 (q, 1, J = 6.6). Anal. Calcd for $C_{12}H_{28}O_2Si_2$: C, 55.32; H, 10.83. Found: C, 55.36; H, 10.77.

Boron Trifluoride Etherate Mediated Reaction of Benzaldehyde with Enol Silane 36. A 25-mL, round-bottomed flask equipped with a nitrogen inlet and a magnetic stirrer was charged with a solution of 0.200 mL (1.97 mmol) of benzaldehyde in 5 mL of CH_2Cl_2. The solution was cooled to −78 °C and 0.24 mL (1.97 mmol) of boron trifluoride etherate was added dropwise. After 10 min, 0.6182 g (2.36 mmol) of enol silane **36** was added with a syringe pump over a 20-min period. The yellow reaction mixture was allowed to stand for 1 h at −78 °C and quenched by the rapid addition of 5 mL of saturated aqueous Na_2CO_3. The mixture was extracted with two 50-mL portions of ether, the combined ether layers were dried ($MgSO_4$), and the solvent was removed with a rotary evaporator to afford 0.6157 g of a crude oil. A 50-mg sample (8.1%) of the crude material was treated with 0.1 mL of *N*-(trimethylsilyl)imidazole in 1 mL of $CDCl_3$ for 15 min at room temperature to afford, after chromatography (silica gel; 19:1 hexane–ethyl acetate), 46.4 mg (83% yield based on benzaldehyde) of a 5:1 mixture of **37** and **38**, respectively: IR (film) 1720, 1500,

(38) Dubois, J. E.; Fellman, P. *Tetrahedron* **1978**, *34*, 1349.

1250 cm^{-1}. Anal. Calcd for $C_{19}H_{34}O_3Si_2$: C, 62.24; H, 9.35. Found: C, 62.05; H, 9.30.

Compound 37: ^{1}H NMR ($CDCl_3$) δ −0.14 (s, 9), 0.17 (s, 9), 0.70 (d, 3, J = 7), 1.38 (s, 3), 1.41 (s, 3), 3.55 (m, 1), 4.70 (d, 1, J = 10), 7.2–7.4 (m, 5).

Compound 38: ^{1}H NMR ($CDCl_3$) δ −0.13 (s, 9), 0.09 (s, 9), 1.21 (d, 3, J = 7), 1.38 (s, 3), 1.41 (s, 3), 3.6 (m, 1), 4.73 (d, 1, J = 9), 7.2–7.4 (m, 5).

Titanium Tetrachloride Mediated Reaction of Benzaldehyde with Enol Silane 36. A 25-mL, round-bottomed flask equipped with a nitrogen inlet and a magnetic stirrer was charged with a solution of 0.200 mL (1.97 mmol) of benzaldehyde and 0.6683 g (2.56 mmol) of enol silane **36** in 5 mL of CH_2Cl_2. The solution was cooled to −78 °C and a solution of 0.22 mL (2.0 mmol) of $TiCl_4$ in 1 mL of CH_2Cl_2 was added with a syringe pump over a 15-min period. After 1 h the bright red reaction mixture was quenched at −78 °C by the rapid addition of 5 mL of saturated aqueous $NaHCO_3$. The mixture was extracted with two 50-mL portions of ether, the combined ether layers were dried ($MgSO_4$), and the solvent was removed with a rotary evaporator to afford 0.6381 g of a crude product. The crude material was taken up in 5 mL of CH_2Cl_2 and this solution was treated with 0.70 g (5.0 mmol) of *N*-(trimethylsilyl)imidazole for 1 h at room temperature. The reaction mixture was dissolved in 50 mL of ether and this solution was washed with two 50-mL portions of water, one 20-mL portion of ice-cold 0.5 M acetic acid, and two 20-mL portions of saturated aqueous $NaHCO_3$. The ethereal solution was then dried ($MgSO_4$) and the solvent was removed with a rotary evaporator to afford 0.5795 g of a crude oil. Chromatography (silica gel; 19:1 hexane–ethyl acetate) afforded 0.5308 g (77%) of a 9:1 mixture of **37** and **38**, respectively.

A 0.0989-g sample of the foregoing mixture of **37** and **38** was dissolved in 2 mL of THF and 0.25 g (1.1 mmol) of periodic acid was added. The solution was allowed to stand at room temperature overnight and was quenched with a slurry of 0.5 g of $NaHSO_3$ in 1 mL of water. After 1 h, the yellow reaction mixture was extracted with three 20-mL portions of ether, and the combined ether layers were dried ($MgSO_4$) and concentrated to a volume of about 5 mL with a rotary evaporator. This solution was treated at room temperature with an excess of ethereal diazomethane for 1 h and the solvent was removed with a rotary evaporator to afford 0.0312 g of a 5:1 mixture of **39** and **40**, respectively.

Compound 39: ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3), 4.70 (d, 1, J = 8). [Lit.[39] ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3), 4.61 (d, J = 8).]

Compound 40: ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3), 5.07 (d, 1, J = 4). [Lit.[39] ^{1}H NMR ($CDCl_3$) δ 3.52 (s, 3), 4.93 (dd, J = 4, 5.5).]

Methyl (3*SR*,4*RS*)-4-(benzyloxy)-3-hydroxypentanoate (44a): ^{1}H NMR ($CDCl_3$) δ 1.21 (d, 3, J = 6.3), 2.52 (d, 1, J = 6.3), 2.54 (m, 1), 3.16 (br s, 1), 3.53 (m, 1), 3.66 (s, 3), 4.01 (m, 1), 4.43 (d, 1, J = 11.6), 4.64 (d, 1, J = 11.6), 7.31 (br s, 5).

Methyl (3*RS*,4*RS*)-4-(benzyloxy)-3-hydroxypentanoate (45a): ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 3, J = 6.3), 2.52 (d, 1, J = 6.3), 2.54 (m, 1), 3.16 (br s, 1), 3.53 (m, 1), 3.66 (s, 3), 4.01 (m, 1), 4.48 (d, 1, J = 11.6), 4.62 (d, 1, J = 11.6), 7.31 (br s, 5).

***tert*-Butyl (3*SR*,4*SR*)- and (3*RS*,4*SR*)-3-Hydroxy-4-(benzyloxy)pentanoate (44b and 45b).** A 1:1.5 mixture of **44b** and **45b** was obtained. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.25; H, 8.50. Small samples of pure **44b** and **45b** were obtained by HPLC (μ-Porasil column; 7:1 hexane–ether).

Compound 44b: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 3, J = 6.3), 1.45 (s, 9), 2.45 (m, 1), 2.93 (d, 1, J = 4.3), 3.52 (m, 1), 3.97 (m, 1), 4.46 (d, 2, J = 11.8), 4.66 (d, 2, J = 11.8), 7.2–7.4 (m, 5); ^{13}C NMR ($CDCl_3$) δ 15.0, 28.0, 38.8, 70.9, 77.2, 80.7, 138.3, 171.6.

Compound 45b: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 3, J = 6.3), 1.45 (s, 9), 2.50 (m, 1), 3.05 (d, 1, J = 3.7), 3.53 (m, 1), 4.00 (m, 1), 4.50 (d, 2, J = 11.7), 4.63 (d, 2, J = 11.7), 7.2–7.4 (m, 5); ^{13}C NMR ($CDCl_3$) δ 15.1, 28.0, 38.1, 70.9, 76.9, 81.0, 138.4, 172.2.

(4*SR*,5*SR*)- and (4*RS*,5*SR*)-2,2-Dimethyl-4-hydroxy-5-(benzyloxy)heptan-3-one (44c and 45c). A 1:1.4 mixture of **44c** and **45c** was prepared by addition of the lithium enolate of pinacolone to 2-(benzyloxy)propanal. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.38; H, 9.06. Small samples of pure **44c** and **45c** were isolated by HPLC (μ-Porasil column; 7:1 hexane–ether).

Compound 44c: ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 9), 1.22 (d, 3, J = 6.3), 2.68 (m, 1), 3.0 (d, 1, J = 4.1), 3.55 (m, 1), 4.07 (m, 1), 4.46 (d, 1, J = 11.8), 4.66 (d, 1, J = 11.8), 7.2–7.4 (m, 5).

Compound 45c: ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 9), 1.23 (d, 3, J = 6.3), 2.70 (m, 1), 3.20 (d, 1, J = 3.8), 3.54 (m, 1), 4.01 (m, 1), 4.52 (d, 1, J = 11.8), 4.65 (d, 1, J = 11.8), 7.2–7.4 (m, 5).

(3*SR*,4*SR*)-4-(Benzyloxy)-3-hydroxy-1-phenylpentan-1-one (44d): ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 3, J = 6.3), 3.06 (d, 1, J = 4.4), 3.15 (d, 2, J = 6.1), 3.63 (dq, 1, J = 4.4, 6.2), 4.24 (m, 1), 4.45 (d, 1, J = 11.8), 4.66 (d, 1, J = 11.8), 7.41 (m, 8), 7.93 (d, 2, J = 7.1); ^{13}C NMR δ 14.8, 40.8, 70.1, 70.8, 76.2, 127.4, 127.6, 128.0, 128.2, 128.4, 133.1, 136.7, 199.8; IR (film) 3480, 1685 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.88; H, 7.09.

(2*S*,3*S*,4*S*)-4-(Benzyloxy)-3-hydroxy-2-methyl-1-phenylpentan-1-one (53): clear oil; ^{1}H NMR ($CDCl_3$) δ 1.30 (d, 3, J = 6.2), 1.32 (d, 3, J = 6.7), 2.27 (d, 1, J = 7.6), 3.54 (qd, 1, J = 6.2, 3.0), 3.70–3.88 (complex, 2), 4.19 (d, 1, J = 11.3), 4.55 (d, 1, J = 11.3), 7.14–7.61 (complex, 8), 7.89–7.95 (complex 2); ^{13}C NMR ($CDCl_3$) δ 14.2, 15.8, 43.4, 70.5, 75.0, 76.2, 127.4, 127.6, 128.1, 128.2, 128.5, 132.9, 136.3, 137.8, 203.6; IR ($CHCl_3$) 3580, 2990, 2950, 2890, 1675, 1600, 1580, 1455, 1375, 1070, 975 cm^{-1}; HRMS calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1572.

(2*R*,3*S*,4*S*)-4-(Benzyloxy)-3-hydroxy-2-methyl-1-phenylpentan-1-one (54): clear oil; ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3, J = 6.8), 1.28 (d, 3, J = 6.3), 3.18 (br s, 1), 3.66 (qd, 1, J = 6.3, 2.2), 3.73–3.83 (complex 2), 4.34 (d, 1, J = 11.8), 4.64 (d, 1, J = 11.8), 7.22–7.59 (complex, 8), 7.90–7.96 (complex, 2); ^{13}C NMR ($CDCl_3$) δ 15.2, 15.7, 42.3, 70.5, 74.4, 77.6, 127.6, 127.9, 128.3, 128.6, 133.0, 136.9, 138.2, 205.0; IR ($CHCl_3$) 3560, 2940, 2880, 1680, 1600, 1580, 1455, 1380, 1070, 975 cm^{-1}; HRMS calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1562.

(2*R*,3*R*,4*S*)-4-(Benzyloxy)-3-hydroxy-2-methyl-1-phenylpentan-1-one (61): clear oil; ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3, J = 7.2), 1.27 (d, 3, J = 6.1), 3.02 (d, 1, J = 2.6), 3.56 (dq, 1, J = 6.9, 6.1), 3.85 (qd, 1, J = 7.2, 4.1), 4.01 (ddd, 1, J = 6.9, 4.1, 2.6), 4.48 (d, 1, J = 11.7), 4.68 (d, 1, J = 11.7), 7.30–7.61 (complex, 8), 7.90–7.96 (complex, 2); ^{13}C ($CDCl_3$) δ 11.8, 15.5, 41.1, 70.5, 74.0, 74.5, 127.6, 127.8, 128.3, 128.4, 128.6, 133.2, 135.6, 138.3, 205.1; IR ($CHCl_3$) 3540, 2990, 2940, 2890, 1670, 1600, 1580, 1455, 1380, 1095, 1075, 980 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.16; H, 7.37.

(2*S*,3*R*,4*S*)-4-(Benzyloxy)-3-hydroxy-2-methyl-1-phenylpentan-1-one (64): clear oil; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, 3, J = 7.3), 1.33 (d, 3, J = 6.1), 3.51 (quintet, 1, J = 6.2), 3.60–3.76 (m, 1), 3.93 (qd, 1, J = 7.3, 4.0), 4.20 (d, 1, J = 11.3), 4.41 (d, 1, J = 11.3), 7.08–7.62 (complex, 8), 7.90–8.95 (complex, 2); ^{13}C NMR ($CDCl_3$) δ 15.6, 15.7, 39.6, 70.7, 76.8, 78.0, 127.5, 127.7, 128.2, 128.4, 128.6, 133.4, 136.5, 138.0, 206.8; IR ($CHCl_3$) 3500, 2990, 2945, 2920, 2890, 1665, 1580, 1455, 1385, 1100, 1075, 985 cm^{-1}; HRMS calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1558.

(4*S*,5*S*,6*S*)-6-(Benzyloxy)-5-hydroxy-2,4-dimethylheptan-3-one (49): clear oil; ^{1}H NMR ($CDCl_3$) δ 1.01 (d, 3, J = 6.9), 1.06 (d, 3, J = 6.9), 1.15 (d, 3, J = 7.0), 1.26 (d, 3, J = 6.2), 2.41 (d, 1, J = 6.5), 2.69 (septet, 1, J = 6.9), 2.94 (quintet, 1, J = 6.9), 3.46 (qd, 1, J = 6.2, 4.2), 3.72 (m, 1), 4.37 (d, 1, J = 11.4), 4.63 (d, 1, J = 11.4), 7.25–7.39 (complex, 5); ^{13}C NMR ($CDCl_3$) 12.5, 16.0, 18.1, 18.4, 39.8, 46.9, 70.8, 75.6, 75.7, 127.8, 128.1, 128.4, 138.2, 217.2; IR ($CHCl_3$) 3540, 2990, 2970, 2890, 1705, 1455, 1385, 1125, 1100, 1075, 1030 cm^{-1}; HRMS calcd for $C_{16}H_{24}O_3$ 264.1726, found 264.1730.

(4*R*,5*S*,6*S*)-6-(Benzyloxy)-5-hydroxy-2,4-dimethylheptan-3-one (50): clear oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3, J = 7.1), 1.03 (d, 3, J = 6.9), 1.08 (d, 3, J = 6.9), 1.27 (d, 3, J = 6.2), 2.67–2.80 (complex, 2), 3.03 (quintet, 1, J = 7.2), 3.56–3.64 (complex, 2), 4.39 (d, 1, J = 11.8), 4.67 (d, 1, J = 11.8), 7.30–7.37 (complex, 5); ^{13}C NMR ($CDCl_3$) δ 14.1, 15.7, 17.8, 18.0, 41.0, 46.6, 70.4, 73.6, 77.2, 127.7, 127.8, 128.3, 138.2, 218.8; IR ($CHCl_3$) 3530, 2980, 2940, 2880, 1710, 1455, 1385, 1075, 1030 cm^{-1}; HRMS calcd for $C_{16}H_{24}O_3$ 264.1726, found 264.1725.

(4*R*,5*R*,6*S*)-6-(Benzyloxy)-5-hydroxy-2,4-dimethylheptan-3-one (62): white solid, mp 38–39 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3, J = 7.2), 1.08 (d, 3, J = 7.0), 1.09 (d, 3, J = 6.9), 1.27 (d, 3, J = 6.1), 2.77 (septet, 1, J = 6.9), 3.00 (br s, 1), 3.11 (qd,

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1, J = 7.2, 3.8), 3.44 (dq, 1, J = 7.0, 6.1), 3.80 (dd, 1, J = 7.0, 3.8), 4.43 (d, 1, J = 11.7), 4.63 (d, 1, J = 11.7), 7.28–7.40 (complex, 5); ^{13}C NMR ($CDCl_3$) δ 10.7, 15.6, 18.0, 18.5, 39.9, 44.3, 70.6, 73.7, 74.4, 127.7, 127.8, 128.4, 138.3, 220.1; IR ($CHCl_3$) 3540, 2980, 2940, 2890, 1700, 1470, 1380, 1070, 1035 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.47; H, 9.43. Found: C, 72.34; H, 9.13.

(4*S*,5*R*,6*S*)-6-(Benzyloxy)-5-hydroxy-2,4-dimethylheptan-3-one (65): clear oil; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 3, J = 6.9), 1.08 (d, 3, J = 7.0), 1.13 (d, 3, J = 7.2), 1.25 (d, 3, J = 6.2), 2.70 (septet, 1, J = 6.9), 3.05 (qd, 1, J = 7.2, 5.3), 3.32 (d, 1, J = 6.8), 3.53 (qd, 1, J = 6.2, 5.0), 3.68 (m, 1), 4.42 (d, 1, J = 11.6) 4.59 (d, 1, J = 11.6), 7.25–7.39 (complex, 5); ^{13}C NMR ($CDCl_3$) 14.8, 14.9, 17.6, 18.0, 41.4, 43.4, 70.8, 76.6, 77.2, 127.6, 128.3, 128.4, 138.3, 220.2; IR ($CHCl_3$) 3540, 2990, 2940, 2880, 1710, 1455, 1385, 1130, 1100, 1050 cm^{-1}; HRMS calcd for $C_{16}H_{24}O_3$ 264.1726, found 264.1718.

General Procedure for the Preparation of Diastereomeric Aldols by Reaction of β-Hydroxy Acids with Phenyllithium. To a solution of the diastereomeric acids (200 mg, 0.83 mmol) in dry ether (11.2 mL) at −78 °C was added dropwise freshly prepared phenyllithium ether (3.86 mL of a 0.87 M solution; 3.36 mmol). The resulting mixture was allowed to come to room temperature with the cooling bath over a 17-h period and was then added by cannula to a solution of saturated aqueous NH_4Cl (10 mL) at 0 °C. The mixture was stirred for 10 min, the layers were separated, and the aqueous phase was extracted with ether (2 × 10 mL). After drying over $MgSO_4$, the combined organics were filtered and concentrated with a rotary evaporator to obtain a yellow oil which was purified by analytical HPLC as previously described to give a mixture of aldols. Application of this procedure to the mixture of β-hydroxy acids **59** and **60**, obtained form periodic acid cleavage of the aldols resulting from reaction of lithium enolate of ketone **58** with aldehyde **43** gave aldols **61** and **53** in a ratio of 2.3:1.0 and a combined yield of 47%. The same procedure applied to the mixture of diastereomeric acids resulting from hydrolysis of the 2,6-dimethylphenyl esters resulting from reaction of the lithium enolate of **63** with aldehyde **43** gave aldols **64**, **61**, **54**, and **53** in a ratio of 2.4:2.2:2.0:1.0 ratio and a total yield of 55%.

General Procedure for the Preparation of Diastereomeric Aldols by Reaction of β-Hydroxy Acids with Isopropyllithium. Application of the foregoing procedure using isopropyllithium (0.92 M) provided **62** and **49** in a ratio of 1.6:1.0 and a total yield of 17% and **65**, **62**, **50**, and **49** in a ratio of 2.3:2.2:2.0:1.0 and total yield of 20%.

(1*R*,2*R*,3*S*,4*S*)-4-(Benzyloxy)-2-methyl-1-phenylpentane-1,3-diol (55). To a solution of lithium aluminum hydride (56 mg, 1.47 mmol) in dry THF (7 mL) at 0 °C was added dropwise a solution of aldol **53** (220 mg, 0.738 mmol) in dry THF (3.5 mL). The suspension was stirred 5 min, after which the cooling bath was removed and the mixture stirred for 2 h. The reaction mixture was cooled in an ice bath and treated sequentially with water (56 μL), 4 N aqueous NaOH (56 μL), and water (168 μL). The resulting suspension was stirred at room temperature for 30 min, $MgSO_4$ was added, and the solution was stirred for a further 1 h. The mixture was filtered through a Celite pad and the solvent was removed to give a viscous oil which solidified upon standing. This material was purified by column chromatography on 20 times its weight of silica gel (230–400 mesh) using 3:1 hexane/ether as the eluant to obtain 22.2 mg of pure diol **55** plus 114.3 mg of a mixture of diols **55** and **56** as white solids, mp 86–92 °C.

Compound 55: ^{1}H NMR ($CDCl_3$) δ 0.83 (d, 3, J = 7.0), 1.15 (d, 3, J = 6.1), 1.85 (m, 1), 3.09 (m, 1), 3.52 (m, 1), 3.72 (br s, 2), 4.42 (d, 1, J = 11.3), 4.68 (d, 1, J = 11.3), 5.00 (d, 1, J = 3.0), 7.20–7.51 (complex, 10); IR (neat) 3450, 2975, 1435, 1340, 1030, 985 cm^{-1}.

(1′*S*,4*S*,5*R*,6*R*)-4-[1-(Benzyloxy)ethyl]-6-phenyl-2,2,5-trimethyl-1,3-dioxane (57). To a solution of diol **55** (22.2 mg, 0.074 mmol) in acetone (1.0 mL) at room temperature were added anhydrous $CuSO_4$ (16 mg, 0.10 mmol) and p-toluenesulfonic acid monohydrate (20 mg, 0.106 mmol). The resulting suspension was stirred for 4 days and then was diluted with water (2 mL) and extracted with ether (3 × 3 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give a yellow oil which was purified by column chromatography on 50 times its weight of silica gel (230–400 mesh) using 10:1 hexane/ethyl acetate as the eluant to provide 9.7 mg (39%) of acetonide **57** as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.61 (d, 3, J = 6.8), 1.14 (d, 3, J = 6.4), 1.56 (s, 3), 1.57 (s, 3), 1.69 (qdd, 1, J= 6.7, 2.3, 2.2), 3.57 (dq, 1, J = 8.1, 6.5), 4.07 (dd, 1, J = 8.2, 2.0), 4.65 (d, 1, J = 11.9), 4.78 (d, 1, J = 11.9), 5.10 (d, 1, J = 2.2), 7.20–7.45 (complex, 10); IR (CHC_3) 3000, 1460, 1390, 1260, 1160, 1105, 1070 cm^{-1}.

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Registry No. **1**, 89043-57-2; **2**, 89043-56-1; **3**, 51425-54-8; **4**, 51425-53-7; **5**, 19980-41-7; **6**, 19980-42-8; **7**, 61878-68-0; **8**, 66323-99-7; **9**, 71268-59-2; **10**, 72658-08-3; **11**, 72658-15-2; **12**, 19980-43-9; **13**, 84784-59-8; **14**, 100-52-7; **15**, 78-84-2; (±)-**16**, 102285-74-5; (±)-**17**, 102285-75-6; (±)-**18**, 102285-76-7; (±)-**19**, 102285-77-8; (±)-**20**, 102285-78-9; (±)-**21**, 102285-79-0; (±)-**22**, 102285-80-3; (±)-**23**, 102285-81-4; (±)-**24**, 102285-82-5; (±)-**25**, 87280-57-7; (±)-**26**, 102285-83-6; (±)-**27**, 102285-84-7; (±)-**28**, 102285-85-8; (±)-**29**, 102285-86-9; (±)-**30**, 102285-87-0; (±)-**31**, 102285-88-1; (±)-**32**, 102285-89-2; (±)-**33**, 102285-90-5; (±)-**34**, 85100-11-4; (±)-**35**, 85100-10-3; **36**, 94989-82-9; (±)-**37**, 102285-91-6; (±)-**38**, 102285-92-7; (±)-**39**, 99210-93-2; (±)-**40**, 99210-95-4; **41a**, 77086-38-5; **41b**, 74786-02-0; **42c**, 17510-46-2; **42d**, 13735-81-4; (±)-**43**, 41954-96-5; (DL)-**44a**, 74262-67-2; (DL)-**44b**, 102285-99-4; (DL)-**44c**, 102340-98-7; (DL)-**44d**, 102286-00-0; (DL)-**45a**, 74262-64-9; (DL)-**45b**, 102285-93-8; (DL)-**45c**, 102341-09-3; **46**, 97416-40-5; **47** (isomer 1), 102285-94-9; **47** (isomer 2), 102286-01-1; **48** (isomer 1), 102285-95-0; **48** (isomer 2), 102286-02-2; **49**, 102285-96-1; **50**, 102340-99-8; **51**, 102341-00-4; **52**, 102341-01-5; **53**, 102341-02-6; **54**, 102341-03-7; **55**, 102285-97-2; **56**, 102341-04-8; **57**, 102285-98-3; **58**, 72507-50-7; **59**, 102341-05-9; **60**, 102418-38-2; **61**, 102418-39-3; **62**, 102341-06-0; **63**, 51233-80-8; **64**, 102341-07-1; **65**, 102341-08-2; EtCOEt, 96-22-0; $Me_2CHCOEt$, 565-69-5; Me_3CCOEt, 564-04-5; PhCOEt, 93-55-0; $EtCO_2Pr$-*i*, 637-78-5; $MeCO_2Me$, 79-20-9; $MeCO_2Bu$-t, 540-88-5; Me_3COMe, 75-97-8; PhCOMe, 98-86-2; 2′,4′,6′-trimethylpropiophenone, 2040-15-5; cyclopentanone, 120-92-3; γ-butyrolactone, 96-48-0; PhLi, 591-51-5; *i*-PrLi, 1888-75-1.