Catalysis of the Mukaiyama Aldol Reaction Using Cationic Zirconocene Complexes

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Introduction

The Mukaiyama aldol reaction between and enol silanes and aldehydes (or acetals) is catalyzed by a variety of conventional Lewis acids.[1] Usually, near stoichiometric amounts of these catalysts must be employed and they are often unsuitable for use with acid-sensitive substrates. More recently, catalysts based on trityl salts or trimethylsilyl triflate have been reported to be effective catalysts for this process when used in catalytic amounts.[1a,f,h]

We recently reported that cationic alkoxide derivatives of zirconium are effective catalysts for the Diels–Alder reaction.[2] In contrast to conventional Lewis acid catalysts, diene polymerization is not observed using these organometallic Lewis acids. It occurred to us that these features might prove advantageous in related reactions catalyzed by Lewis acids.

We now report that these compounds are effective catalysts of the Mukaiyama aldol reaction at reasonably low catalyst loadings (5–10 mol%).[3a] The results obtained differ significantly from those reported where an isoelectronic organolanthanide catalyst was employed.[3b]

More recently, the use of $Cp_2Zr(OTf)_2(THF)$ as a catalyst for the Mukaiyama aldol reaction between enol silanes and aldehydes or ketones at room temperature has been reported.[3c] In that study, the issue of simple diastereoselection was not thoroughly addressed, as in the present work.

Results and Discussion

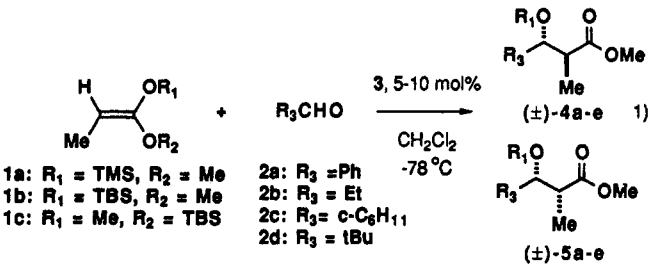
The aldol reactions between enol silanes (**1a–e**) and aldehydes (**2a–d**) were conducted in the presence of 10 mol% of $[Cp_2Zr(O^tBu)THF][BPh_4]$ (**3**) in dichloromethane solution and the results obtained are summarized in Table I (eq 1).

Using enol silane **1a** (1.2 equiv) and benzaldehyde, a high yield of the 2,3-anti and 2,3-syn cross-aldol products (**4a** and **5a**, respectively) was obtained at room temperature (entry 1). With aliphatic aldehydes, a large excess of enol silane **1a** was required for complete reaction (entries 2 and 3).

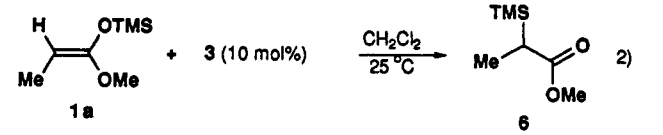
Table I. Aldol Reactions Catalyzed by $[Cp_2Zr(O^tBu)THF][BPh_4]$[a]

entry	enol silane	E/Z[b]	aldehyde	T (°C)	t (h)	yield (%)[c]	4/5[d]
1	1a	6.7:1	2a	25	1	95	1.1:1
2[e]	1a	6.7:1	2c	25	1	93	1.1:1
3[e]	1a	6.7:1	2b	25	1	91	1.4:1
4	1a	6.7:1	2a	−78	1	98	1.28:1
5	1a	6.7:1	2b	−78	1	90	1.74:1
6	1a	6.7:1	2c	−78	1	94	1.21:1
7	1a	6.7:1	2d	−78	1	96	1:1.92
10	1b	5.2:1	2a	−78	1	88	1.33:1[f]
11	1c	1:4.6	2a	−78	1	85	1.20:1[f]

[a] All reactions were conducted in dichloromethane solution using 1.25 mmol of the enol silane, 1.0 mmol of aldehyde, and 0.05–0.10 mmol of $[Cp_2Zr(O^tBu)THF][BPh_4]$ unless otherwise noted. [b] Ratios determined by ^1H NMR. [c] Isolated yields. [d] Ratios determined by GC (**4b–e**; **5b–e**) or ^1H NMR (**4a**; **5a**); assignments are based on deprotection of the *O*-silyl products and comparison of the ^1H and ^{13}C NMR spectra of the known β-hydroxy esters (**7a–d**; **8a–d**) to literature data.[12–14] [e] An amount of 2.5 mmol of enol silane was employed. [f] Assignment of relative stereochemistry is tentative but is based on the very close analogy between the spectral characteristics of **4e** and **5e** to their trimethylsilyl analogs **4a** and **5a** (see Experimental Section for details).



We noted in these reactions that enol silane **1a** was being consumed by a process unrelated to aldol condensation. In fact, the major product obtained under these conditions was the *C*-silyl ester **6** (eq 2).[4a] This isomerization process is catalyzed by compound **3**. In the absence of aldehyde, enol silane **1c** was quantitatively converted to **6** at room temperature in the presence of 10 mol% of compound **3**.[4b] As the *C*-silyl ester **6** does not engage in aldol condensations with aldehydes under these conditions, we reasoned that the excess of enol silane required at room temperature was a reflection of the competing conversion of this compound to **6**.



Fortunately, this problem could be entirely alleviated by conducting the reaction at low temperatures (entries 4–7). Under these conditions, isomerization of **1a** to compound **6** does not occur at a competitive rate and high yields of the cross-aldol product are obtained using a slight excess of the enol silane.

(1) For a review of this and related processes see (a) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. See also (d) Kagan, H. B. *Inorg. Chim. Acta* **1987**, *140*, 3. (e) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027. (f) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1985**, 447. (g) Heathcock, C. H.; Hug, K. T.; Flippin, L. A. *Tetrahedron Lett.* **1984**, *25*, 5973. (h) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759. (i) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Ibid.* **1979**, *20*, 4029. (j) Mukaiyma, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

(2) (a) Collins, S.; Koene, B. K.; Ramachandran, R.; Taylor, N. J. *Organometallics* **1991**, *10*, 2092. (b) Collins, S.; Hong, Y.; Kuntz, B. K. *Ibid.* **1993**, *12*, 964.

(3) (a) Presented in part at the Gordon Research Conference on Organometallic Chemistry, Newport, RI, July, 1992. (b) Gong, L.; Streitweiser, A. *J. Org. Chem.*, **1990**, *55*, 6235. (c) Hollis, T. K.; Robinson, N. P., Bosnich, B. *Tetrahedron Lett.* **1992**, *33*, 6423.

(4) (a) Lutsenko, I. F., Baukov, Y. I.; Burlachenko, G. S.; Khasapov, B. N. *J. Organomet. Chem.* **1966**, *5*, 20. (b) The mechanism of this isomerization process is not clear at present but does not appear to involve zirconocene enolate complexes (either neutral or cationic[16]) as intermediates.

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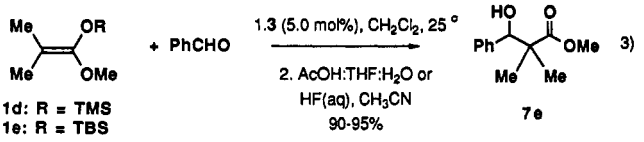
As noted in Table I, the stereoselectivity of this process is modest and dependent on the structure of the aldehyde employed.[5] The least sterically hindered aldehyde (**2b**) reacts with enol silane **1a** to provide the anti stereoisomer **4b** (entries 3 and 5) whereas pivaldehyde (**2d**) reacted with **1a** to provide the syn stereoisomer **5d** as the major product (entry 7)! The level of selectivity was only marginally improved at lower temperatures (e.g. entries 1 vs 4 and 3 vs 5).

To investigate the dependence of the stereoselectivity on enol silane geometry, we conducted reactions using *tert*-butyldimethylsilyl ketene acetals **1b** or **1c** (entries 10 and 11).[6a] As can be seen from the results, the stereoselectivity was essentially independent of enol silane geometry although the *E*-isomer was slightly more selective than the *Z*-isomer.[6b]

Finally, we note that this reaction is not restricted to trisubstituted enol silanes **1a–c**. The reaction between benzaldehyde and either trimethylsilyl enol ether **1d** or its *tert*-butyldimethylsilyl analog **1e** (eq 3) afforded high yields of the cross-aldol product **7e** following deprotection.



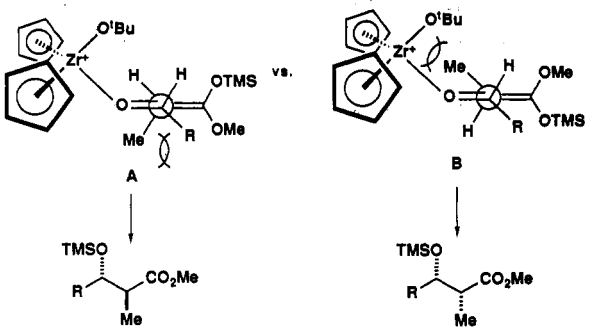
These results differ significantly from those recently reported by Gong and Streitweiser.[3a] In that study, an isoelectronic lanthanide catalyst was employed [Cp''_2YbCl; Cp'' = 1,3-$(TMS)_2Cp$] and the use of stoichiometric amounts of TMSCl were required for turnover, presumably by converting Yb alkoxide products to silyl ethers and the active catalyst.

In the former study, only aromatic aldehydes reacted cleanly under the conditions developed, and the level of stereoselectivity was improved from that observed here and dependent on enol silane geometry. A cyclic transition state was proposed to account for the results.

It seems unlikely that a similar transition state can be invoked here given the lower stereoselectivity observed and the insensitivity of the diastereoselection to enol silane geometry. Indeed, it seems unreasonable to invoke simultaneous complexation of both the aldehyde and the enol silane to the metal center in the present system (cf. ref 3a), especially in view of the fact that we have structural evidence that the *tert*-butoxide ligand in **3** (and presumably in related complexes) functions as a four-electron donor.[2]

We believe that the present reactions are proceeding through acyclic transition states involving the metallocene-coordinated aldehyde.[7] Acyclic transition states have been postulated for reactions of e.g. TAS enolates with aldehydes[8] or in the reactions of enol silanes with acetals catalyzed by trimethylsilyl triflate.[1a] In these cases, it is the syn stereoisomer that is selectively produced and the sense of diastereoselectivity is independent of enolate

Scheme I



geometry. In the present case, however, sterically unhindered aldehydes exhibit a preference for the anti stereoisomer. As shown in Scheme I, one would expect this result if the steric interaction between the methyl group of the enol silane and the ligands on zirconium is of comparable importance to vicinal repulsion between the aldehyde substituent and this methyl group in the two acyclic transition states (i.e. **A** vs **B**). This hypothesis accounts for the insensitivity of enol silane geometry to the stereochemical outcome of the reaction: the more sterically hindered aldehydes exhibit lowered anti selectivity, and syn selectivity is observed in the case of pivaldehyde. In the latter case, one might expect vicinal repulsion between the *tert*-butyl group and the methyl group of the enol silane to partially override the interaction of this substituent with the ligands on zirconium.[9]

A similar hypothesis has also been advanced to account for the anti selectivity observed when this process is catalyzed by trityl perchlorate.[1f] However, in this case, a significant improvement in anti selectivity was noted when using *tert*-butyldimethylsilyl enol ethers compared with their trimethylsilyl analogs, an effect that is not seen here. While it is clear that cationic zirconocene compounds are efficient catalysts for this process, the stereoselectivity observed using catalyst **3** is not high enough for synthetic use. We are currently investigating whether use of more sterically hindered catalysts analogous to e.g. Cp''_2YbCl leads to improved stereoselectivity.[10]

Experimental Section

All chemicals were reagent grade and purified as required. Tetrahydrofuran, hexanes, diethyl ether, and toluene were all dried and deoxygenated by distillation from sodium–benzophe-

(5) The ratios observed were obtained under conditions of kinetic control; exposure of pure *syn*-**4a** to the reactions conditions did not lead to significant isomerization at −78 °C.

(6) (a) Ireland, R. E.; Mueller, R. H.; Wilard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Isomerization of **1b** or **1c** is not observed under these conditions.

(7) Admixture of *p*-tolualdehyde (1.0 equiv) and compound **3** in CD_2Cl_2 at −78 °C resulted in the formation of a bright yellow aldehyde complex with liberation of coordinated THF: ^1H NMR (200 MHz, CD_2Cl_2, 196 K) 9.59 (s, 1H, CHO), 7.77 (AA′ d, J = 8.1 Hz, 2H, *o*-CH) 7.40 (BB′ d, J = 8.1 Hz, 2H, *m*-CH) superimposed on 7.35 (br m, 8H, BPh_4), 7.06 (t, J = 7.1 Hz, 8H, BPh_4), 6.91 (t, J = 7.1 Hz, 4H, BPh_4) 6.35 (s, 10H, CpH), 3.60 (m, 4H, free THF), 2.46 (s, 3H, p-CH_3), 1.82 (m, 4H, free THF), 1.26 (s, 9H, tBu). NOE difference ^1H NMR spectra of this aldehyde complex revealed the presence of positive enhancements for the ortho-aromatic protons (8.3%), Cp protons (1.9%), and *tert*-butyl protons (1.4%) on irradiation of the aldehyde proton, consistent with the conformation depicted in the Scheme I being favored on a time-averaged basis.[2b]

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

(9) Consistent with the hypothesis that differential steric interactions of the aldehyde substitutent with either the metal center or the enol silane in the transition state are responsible for the origins of the selectivity observed in all cases, a linear correlation (R = 0.97) between log[anti/syn] and Taft's steric parameter (E_s^0)[17] was obtained for the aliphatic aldehydes studied.

(10) For example, the use of catalytic amounts of optically pure [1,2-ethylenebis(η^5-tetrahydroindenyl)zirconium(*tert*-butoxide)(THF)] [BPh_4][2b] in this process led to little change in diastereoselectivity (e.g. **4a/5a** = 1.2:1 and **4b/5b** = 1.5:1 at −78 °C) but with marginal enantioselectivity (<20% ee). S. Collins, unpublished results.

none ketyl. Dichloromethane was dried by distillation from calcium hydride. All reactions were conducted under an atmosphere of dry N_2 using standard techniques.

Compounds **1a–e** were prepared using literature procedures.[6,11] Compound **3** was prepared as described in the literature.[2]

^1H and ^{13}C NMR spectra were obtained on a Bruker AM-250 or AC-200 spectrometer. Chemical shifts are referenced to residual undeuterated solvent. IR spectra were recorded on a Bomem MB-100 FT-IR instrument. High- and low-resolution mass spectra were measured on a KRATOS MSX-90 instrument at the University of Guelph. Some of the silyl aldol products prepared failed to give discernible molecular ions or had strong (M – 1) fragments under electron impact or chemical ionization; HRMS are reported for the (M – 15) ions.

GC analyses were conducted on a Hewlett-Packard 5890A instrument equipped with a 30 m × 0.25 mm J & W Scientific DB-1701 capillary column and were used to determine diastereomer ratios in conjunction with NMR data. Retention times for **4b–e** and **5b–e** are summarized below (40 °C, 2 min; 20 °C/min; 200 °C, 15 min):

compound	t_R (min)	compound	t_R (min)
4b	8.09	**4d**	8.88
5b	8.16	**5d**	8.82
4c	10.80	**4e**	12.43
5c	10.83	**5e**	12.52

Mukaiyama Aldol Reactions. Representative Procedure. Preparation of 2,3-*anti*- and 2,3-*syn*-Methyl 2-Methyl-3-phenyl-3-(trimethylsiloxy)propanoate (4a and 5a). Benzaldehyde (120 μL, 1.18 mmol) was added via syringe to a solution of compound **3** (40 mg, 0.058 mmol) in CH_2Cl_2 (3.0 mL) at –78 °C. The solution turned bright yellow in color. Enol silane **1a** (227 mg, 1.42 mmol) was then added in one portion via syringe. The bright yellow color of the solution gradually faded, and after 1 h at –78 °C GC analysis indicated complete consumption of benzaldehyde. To isolate the products, the mixture was diluted with dry *n*-pentane (to precipitate compound **3**) and filtered through Celite, washing with *n*-pentane. The filtrate was concentrated to dryness in vacuo at 15 mmHg to provide crude product which could be further purified by flash chromatography on silica gel eluting with hexanes–ether 95:5 to provide compounds **4a** and **5a** (308.8 mg, 98% yield): IR (thin film) 3064, 3030, 2956s, 2895, 1738s, 1494, 1455s, 1435s, 1363, 1255s, 1196s, 1167s, 1076s, 1028, 986, 882s, 843s, 756s, 702s, 624 cm^{-1}. **4a**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.69 (d, J = 9.4 Hz, 1H), 3.73 (s, 3H), 2.72 (pseudo quint, $J \sim 6$ Hz, 1H), 0.86 (d, J = 7.0 Hz, 3H), –0.05 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 175.6, 142.0, 128.1, 127.9, 126.9, 77.6, 51.3, 49.1, 13.7 (anti-CH_3), –0.18 (3C). **5a**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.00 (d, J = 5.9 Hz, 1H), 3.56 (s, 3H), 2.74 (pseudo quint, $J \sim 6$ Hz, 1H), 1.13 (d, J = 6.9 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.5, 143.0, 127.7, 127.2, 126.1, 75.6, 51.2, 48.7, 11.4 (*syn*-CH_3), –0.18 (3C); HRMS calcd for $C_{14}H_{22}O_3Si$: 266.13381, found (EI) 266.13427. The ratio of **4a/5a** was determined by integration of the resonances at 4.69 and 5.00 ppm in the ^1H NMR spectrum (1.28:1).

Spectral data for the compounds prepared are summarized below:

2,3-*anti*- and 2,3-*syn*-Methyl 2-Methyl-3-(trimethylsiloxy)pentanoate (4b and 5b). IR (thin film) 2959s, 2882, 1738s, 1460, 1437, 1372, 1305, 1254s, 1197s, 1174s, 1114s, 1053s, 1018s, 922, 889s, 846s, 752, 687 cm^{-1}. **4b**: ^1H NMR (200 MHz, $CDCl_3$) δ 3.90 (pseudo q, $J \sim 6$ Hz, 1H), 3.67 (s, 3H), 2.60 (pseudo quint, $J \sim 7$ Hz, 1H), 1.47 (pseudo quint, $J \sim 7$Hz, 2H), 1.07 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.6, 75.0, 51.3, 45.7, 26.1, 12.6 (*anti*-CH_3), 8.9, 0.19 (3C). **5b**: ^1H NMR (200 MHz, $CDCl_3$) δ 3.86 (8 line m, 1H), 3.67 (s, 3H), 2.50 (qd, J = 7.0, 5.6 Hz, 1H), 1.47 (pseudo quint, $J \sim 7$ Hz, 2H), 1.13 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.5, 74.7, 51.3, 44.7, 28.1, 11.6, 9.8 (*syn*-CH_3), 0.27 (3C); HRMS calcd for $C_{10}H_{22}O_3Si$–CH_3 203.11034, found (EI) 203.10972.

2,3-*anti*- and 2,3-*syn*-Methyl 3-Cyclohexyl-2-methyl-3-(trimethylsiloxy)propanoate (4c and 5c). IR (thin film) 2932s, 2854s, 1736s, 1454s, 1435s, 1365, 1314, 1253s, 1197s, 1170s, 1114s, 1066s, 1026s, 988, 971, 904s, 847s, 752s, 688, 637 cm^{-1}. **4c**: ^1H NMR (250 MHz, $CDCl_3$) δ 3.76 (dd, J = 6.4, 4.9 Hz, 1H), 3.67 (s, 3H), 2.66 (m, 1H), 1.8–1.4 (complex m, 6H), 1.12 (d, J = 7.0 Hz, 3H) superimposed on 1.4–0.95 (complex m, 5H) 0.09 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.0, 78.8, 51.2, 42.6, 40.0, 13.7 (*anti*-CH_3), 0.46 (3C) + 10 signals at 30.7, 29.9, 28.6, 26.6, 26.5, 26.4, 26.3, 26.25, 26.16, 26.0 ppm due to nonequivalent CH_2 carbons on the cyclohexane ring that could not be unambiguously assigned to either isomer. **5c**: ^1H NMR (250 MHz, $CDCl_3$) δ 3.71 (pseudo t, J = 4.3 Hz, 1H), 3.68 (s, 3H), 2.66 (m, 1H), 1.8–1.4 (complex m, 6H), 1.07 (d, J = 7.1 Hz, 3H), superimposed on 1.4–0.95 (complex m, 5H), 0.09 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 175.8, 78.2, 51.2, 44.3, 41.9, 11.1 (*syn*-CH_3), 0.52 (3C); HRMS calcd for $C_{14}H_{28}O_3Si$–CH_3 257.15729, found (EI) 257.15681.

2,3-*anti*- and 2,3-*syn*-Methyl 2,4,4-Trimethyl-3-(trimethylsiloxy)pentanoate (4d and 5d). IR (thin film) 2958s, 2907, 1738s, 1461, 1435, 1396, 1364, 1315, 1252s, 1196s, 1173s, 1090s, 1072s, 1034s, 951, 927, 894s, 844s, 752, 684 cm^{-1}. **4d**: ^1H NMR (250 MHz, $CDCl_3$) δ 3.64 (s, 3H), 3.37 (d, J = 4.4 Hz, 1H), 2.76 (qd, J = 7.2, 4.4 Hz, 1H), 1.18 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H) 0.11 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.8, 83.6, 51.0, 42.9, 36.3, 26.4 (3C), 16.8 (*anti*-CH_3), 0.57 (3C). **5d**: ^1H NMR (250 MHz, $CDCl_3$) δ 3.78 (d, J = 4.2 Hz, 1H), 3.66 (s, 3H), 2.65 (qd, J = 7.1, 4.2 Hz, 1H), 1.12 (d, J = 7.1 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.9, 79.8, 51.4, 41.2, 36.3, 26.4 (3C), 13.2 (*syn*-CH_3), 0.41 (3C); HRMS calcd for $C_{12}H_{26}O_3Si$–CH_3 231.14164, found (EI) 231.14055.

2,3-*anti*- and 2,3-*syn*-Methyl 3-(*tert*-Butyldimethylsiloxy)-2-methyl-3-phenylpropanoate (4e and 5e). IR (thin film) 3065, 3030, 2945s, 2891s, 2858s, 1739s, 1494, 1460s, 1435s, 1363s, 1255s, 1196s, 1168s, 1078s, 1027s, 1006, 925, 908, 849s, 777s, 702s, 694 cm^{-1}. **4e**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.28 (m, 5H), 4.70 (d, J = 9.3 Hz, 1H), 3.72 (s, 3H), 2.8–2.6 (m, 1H), 0.88 (s, 9H), 0.85 (d, J = 7.1 Hz, 3H), –0.02 (s, 3H), –0.30 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 175.6, 142.2, 128.1, 127.8, 127.0, 77.8, 51.4, 49.2, 25.7 (3C), 17.9, 13.7 (*anti*-CH_3), –4.8, –5.5. **5e**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.02 (d, J = 5.6 Hz, 1H), 3.57 (s, 3H), 2.8–2.6 (m, 1H), 1.14 (d, J = 7.0 Hz, 3H), 0.80 (s, 9H), 0.01 (s, 3H), –0.21 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.5, 143.1, 127.7, 127.2, 126.3, 75.8, 51.3, 49.0, 25.5 (3C), 18.1, 11.3 (*syn*-CH_3), –4.6, –5.4. HRMS calculated for $C_{17}H_{28}O_3Si$–CH_3 293.15729, found (EI) 293.15675.

Conversion of Compounds 4a–d and 5a–d to Aldol Products 7a–e and 8a–d. Deprotection was accomplished by stirring the purified product in 10 mL of acetic acid–THF–H_2O (8:8:1) at room temperature for ~4–7 h. The solution was diluted with ether (20 mL), and washed with water (3 × 10 mL), saturated $NaHCO_3$ solution (3 × 10 mL) and brine (10 mL), and the organic phase was dried over Na_2SO_4. Filtration followed by concentration of the filtrate in vacuo provided a mixture of the two aldol products that could be purified by flash chromatography on silica gel (previously deactivated by flushing with "wet" THF) eluting with hexane–ether 1:1.

2,3-*anti*- and 2,3-*syn*-Methyl 3-Hydroxy-2-methyl-3-phenylpropanoate (7a and 8a).[12] **7a**: ^1H NMR (250 MHz, $CDCl_3$ with 1% HCO_2H) δ 7.34 (br m, 5H), 4.78 (d, J = 8.7 Hz, 1H), 3.74 (s, 3H), 2.85 (pseudo quint, J ~7.5 Hz, 1H), 1.01 (d, J = 7.2 Hz, 3H). **8a**: ^1H NMR (250 MHz, $CDCl_3$ with 1% HCO_2H) δ 7.32 (br m, 5H), 5.12 (d, J = 4.2 Hz, 1H), 3.68 (s, 3H), 2.85 (pseudo quint, J ~7.5 Hz, 1H), 1.18 (d, J = 7.2 Hz, 3H).

2,3-*anti*- and 2,3-*syn*-Methyl 3-Hydroxy-2-methylpentanoate (7b and 8b).[12,14] **7b**: ^1H NMR (250 MHz, $CDCl_3$ with 1% HCO_2H) δ 3.71 (s, 3H), 3.64 (8 line m, 1H), 2.58 (pseudo quint, $J \sim 7$ Hz, 1H), 1.65–1.35 (complex m, 2H), 1.25 (br s, 1H), 1.18 (d, J = 7.3 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.7, 74.7, 51.8, 44.9, 27.6, 14.2 (*anti*-CH_3), 9.9. **8b**: ^1H NMR (250 MHz, $CDCl_3$ with 1% HCO_2H) δ 3.86 (8 line

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m, 1H), 3.71 (s, 3H), 2.58 (pseudo q, $J \sim 7$ Hz, 1H), 1.65–1.35 (complex m, 2H), 1.21 (d, $J = 7.3$ Hz, 3H), 0.96 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.5, 73.4, 51.8, 44.0, 26.9, 10.7 (*syn*-CH_3), 10.4.

2,3-*anti*- and 2,3-*syn*-Methyl 3-Cyclohexyl-3-hydroxy-2-methylpropanoate (7c and 8c).[13] **7c**: ^{1}H NMR (250 MHz, $CDCl_3$ with 1% HCO_2H) δ 3.72 (s, 3H), 3.43 (pseudo t, $J \sim 6$ Hz, 1H), 2.73 (m, 1H), 2.0–1.5 (complex m, 7H), 1.22 (d, $J = 7.1$ Hz, 3H), superimposed on 1.5–0.9 (complex m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.9, 77.6, 51.55, 41.8, 40.9 and 14.7 (*anti*-CH_3) ppm with seven signals at 29.9, 29.0, 28.9, 26.8, 26.3 (~3C), 26.0 (~2C), and 25.8 due to CH_2 carbons in the cyclohexane ring that could not be unambiguously assigned to either isomer. **8c**: ^{1}H NMR (250 MHz, $CDCl_3$ with 1% HCO_2H) δ 3.72 (s, 3H), 3.69 (d, $J \sim 7.2$, 3.3 Hz, 1H), 2.73 (m, 1H), 2.0–1.5 (complex m, 7H), 1.16 (d, $J = 7.1$ Hz, 3H) superimposed on 1.5–0.9 (complex m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$), 176.7, 75.6, 51.6, 41.2, 40.1, and 9.9 (*syn*-CH_3).

2,3-*anti*- and 2,3-*syn*-Methyl 3-Hydroxy-2,4,4-trimethylpentanoate (7d and 8d).[14] **7d**: ^{1}H NMR (250 MHz, $CDCl_3$ with 1% HCO_2H) δ 3.69 (s, 3H), 3.28 (d, $J = 2.0$ Hz, 1H), 2.74 (qd, $J = 7.0, 2.0$ Hz, 1H), 1.35 (d, $J = 7.0$ Hz, 3H), 0.89 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.9, 82.6, 51.7, 38.4, 36.0, 26.1 (3C), 18.0 (*anti*-CH_3). **8d**: ^{1}H NMR (250 MHz, $CDCl_3$ with 1% HCO_2H) δ 3.69 (s, 3H) superimposed on 3.68 (d, $J = 3.5$ Hz, 1H), 2.76 (pseudo quint, $J \sim 6$ Hz, 1H), 1.24 (d, $J = 7.1$ Hz, 3H), 0.94 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.5, 78.2, 51.7, 41.1, 35.5, 26.4 (3C), 12.9 (*syn*-CH_3).

Methyl 3-Hydroxyl-2,2-dimethyl-3-phenylpropanoate (7e).[15] This compound was prepared from the reaction of either enol silane **1d** or **1e** with benzaldehyde, followed by deprotection of the silylated aldol product as described above in the case of **1d** or by treatment with aqueous hydrofluoric acid in acetonitrile[18] in the case of **1e**: ^{1}H NMR (250 MHz, $CDCl_3$) 7.29 (m, 5H), 4.92 (d, $J = 2.5$ Hz, 1H), 3.74 (s, 3H), 3.0 (br d, $J = 2.5$ Hz, 1H, D_2O exchangeable), 1.13 (s, 3H), 1.08 (s, 3H).

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