Notes

Highly 1,4-Syn Diastereoselective, Phosphoramide-Catalyzed Aldol Additions of Chiral Methyl Ketone Enolates†

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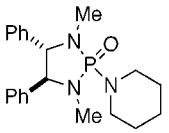
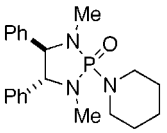
Recent reports from these laboratories have disclosed the design and development of a new class of asymmetric aldol additions catalyzed by chiral Lewis bases.[1] In particular, the stilbenediamine-derived phosphoramide **1**[1a] has emerged as a highly selective and general catalyst for the aldol addition of trichlorosilyl enolates of ketones to aldehydes. This transformation is believed to involve a closed, chairlike transition structure with enolate, aldehyde, and phosphoramide organized around a hexacoordinate silicon center.[1b] The addition of enolates bearing a stereogenic center is clearly of great importance in the application of the aldol addition to synthesis. Although general success has been realized with chiral propanoate/ethyl ketone systems,[2] the related methyl ketone substrates have been less thoroughly investigated.[3] Given our recent report of enantioselective aldol additions with methyl ketone-derived enolates[1d,4] and our hypothesis that the reaction takes place via a closed transition structure, we investigated the feasibility of using *chiral* methyl ketones in conjunction with the catalyst **1** to afford protected 1,4-dihydroxypentanones.

Synthesis of the requisite substrates proceeded according to literature precedent. Protection of (*S*)-methyl lactate,[5] followed by addition of MeLi at −110 °C[6] and silylation with TMSOTf and Et_3N in benzene,[3d] provided the TMS enol ethers **3a**−**c** in good overall yield, Scheme



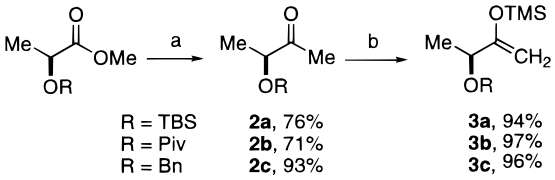
(*S*,*S*)-**1**



(*R*,*R*)-**1**

1. We recently reported that treatment of TMS enol

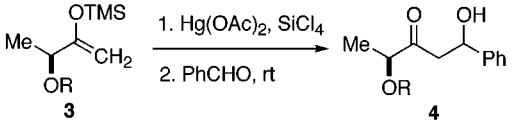
Scheme 1[a]



[a] Key: (a) MeLi/TMSCl/THF/Et_2O/−110 °C; (b) TMSOTf/Et_3N/PhH/0 °C.

ethers with 2 equiv of $SiCl_4$ and 1 mol % $Hg(OAc)_2$ cleanly provides the corresponding trichlorosilyl enolates in good yield.[1d,4] In the current studies, we briefly investigated even lower catalyst loading, and found that although 0.25 mol % was effective, the reaction was somewhat slower (4−5 h), especially starting from **3b** or **3c**. After 1 h reaction was complete and removal of the volatile components provided the crude trichlorosilyl enolate, which could be used directly in aldol reactions. Thus, addition of CH_2Cl_2 and benzaldehyde led to the formation of aldol adducts **4** in 8 h at room temperature, Table 1. The

Table 1. Uncatalyzed Additions of Trichlorosilyl Enolates to Benzaldehyde[a,b]



3 **4**

entry	R	$Hg(OAc)_2$ (mol %)	products	syn/anti	yield, %
1	TBS	0.25	**4a**	1/1.2[c]	82
2	Piv	0.5	**4b**	1/2.4[d]	71
3	Bn	0.5	**4c**	1/3.4[d]	75

[a] 2.0 equiv of $SiCl_4$/1 M CH_2Cl_2/1 h. [b] 1.0 equiv of PhCHO/1 M CH_2Cl_2/8 h. [c] Determined by CSP SFC analysis. [d] Determined by ^1H NMR analysis.

products were isolated as mixtures of diastereomers in good yield with poor diastereoselectivity, favoring the anti product. The assignment of configuration is based on an X-ray crystal structure of *syn*-**4b**; other assignments were made by deprotecting and correlating the syn and anti diols to the established pivalate-derived diol. The lack of selectivity was somewhat surprising as we (and others)[7] have previously asserted that uncatalyzed reactions of such silyl enolates proceed through closed,

† The Chemistry of Trichlorosilyl Enolates. 8.

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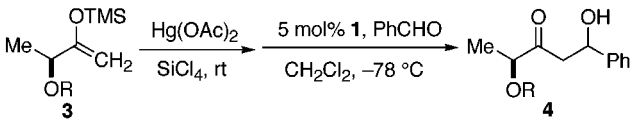
Table 2. Catalyzed Additions of Trichlorosilyl Enolates to Benzaldehyde[a,b]



entry	R	$Hg(OAc)_2$ (mol %)	catalyst	products	syn/anti	yield, %
1	TBS	0.5	(*S*,*S*)-**1**	**4a**	1.5/1[c]	85
2	Piv	1	(*S*,*S*)-**1**	**4b**	3.4/1[d]	78
3	Bn	1	(*S*,*S*)-**1**	**4c**	1/1.1[d]	78
4	TBS	0.5	(*R*,*R*)-**1**	**4a**	73/1[c]	85
5	Piv	1	(*R*,*R*)-**1**	**4b**	20/1[d]	78
6	Bn	1	(*R*,*R*)-**1**	**4c**	11/1[d]	77

[a] 2.0 equiv of $SiCl_4$/1 M CH_2Cl_2/1 h. [b] 1.0 equiv of PhCHO/5 mol % **1**/0.5 M CH_2Cl_2/3 h. [c] Determined by CSP SFC analysis. [d] Determined by ^1H NMR analysis.

boatlike transition structures where good information transfer from the resident stereogenic center on the enolate was expected.

Attempts were made to control the diastereoselectivity of the process by using 5 mol % of (*S*,*S*)-**1**. Although rates were accelerated (reaction time: 2−3 h at −78 °C) and good yields of aldol adducts were obtained, poor diastereoselectivities were again observed, Table 2, entries 1−3. It was also surprising that the syn diastereomer predominated, since in achiral enolate systems (*S*,*S*,)-**1** preferentially produces the *S*-aldol adducts, which would correspond to the anti diastereomer in the present series. These catalyzed reactions are envisioned to proceed through closed, chairlike transition structures organized around a hexacoordinate silicon atom. The combination of the stereogenic center on the enolate backbone and the hexacoordinate arrangement of groups around silicon apparently favors formation of the syn diastereomer even though the intrinsic selectivity of the catalyst is for formation of the epimeric adduct.

The enantiomeric catalyst, (*R*,*R*)-**1**, was next employed in anticipation that its preference for forming the *R*-aldol adduct combined with the same intrinsic preference of the substrates (in the catalyzed reactions) would lead to high selectivity. Indeed, this was found to be the case. When 5 mol % of (*R*,*R*)-**1** was used, high syn selectivity was observed for all substrates, Table 2, entries 4−6. The highest selectivity was realized with the silyl enol ether **3a**, providing the aldol adducts in a 73/1 syn/anti ratio. Apparently, this represents a "matched case" of double stereodifferentiation.[8]

The reduced yields of these reactions were disturbing since the pure, isolated trichlorosilyl enolates provide adducts in greater than 90% yield in almost all cases. We thought the problem might lie in the mercury-catalyzed metathesis reaction as a modest amount (10−15%) of the bis(enoxy)dichlorosilane is formed, along with the desired mono(enoxy)trichlorosilane. As the bis(enoxy)dichlorosilanes are much less reactive than the corresponding enoxytrichlorosilanes in the aldol addition, we were confident that their formation would have no bearing on the *selectivities* of the in situ reactions, though the maximum *yields* were effected. To confirm that the reactions under study here were also clean and efficient, we prepared and purified the trichlorosilyl enolate derived from **3a** and used it in an aldol reaction with (*R*,*R*)-**1** as the catalyst, Scheme 2. The aldol adduct *syn*-**4a** was isolated with excellent syn-diastereoselectivity (70/1) and in very good yield.

Scheme 2

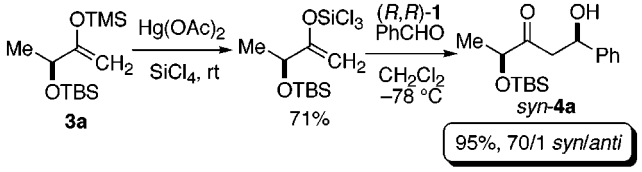
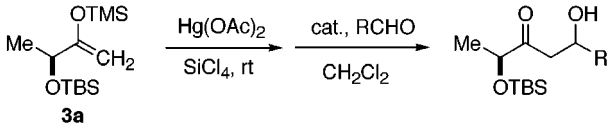


Table 3. Aldol Additions with TMS Enol Ether 3a



entry	R	cat.	T, °C	products	syn/anti	yield, %
1	C_6H_{11}	none	rt	**5**	1/3[c]	55
2	(*E*)-CH=CHCH$_3$	none	rt	**6**	2.3/1[d]	66
3	(*E*)-CH=CHCH$_3$	(*S*,*S*)-**1**	−78	**6**	1.3/1[d]	80
4	(*E*)-CH=CHCH$_3$	(*R*,*R*)-**1**	−78	**6**	6.2/1[d]	81

[a] 0.5 mol % $Hg(OAc)_2$/2.0 equiv of $SiCl_4$/1 M CH_2Cl_2/1 h. [b] 1.0 equiv of RCHO/5 mol % **1**/0.5 M CH_2Cl_2/3 h. [c] Determined by ^1H NMR analysis. [d]Determined by CSP SFC analysis of the corresponding benzoate.

In the hope that such trends were general, the addition of the TBS-protected enolate to other aldehydes was briefly investigated. Unpromoted reactions were, as before, unselective with either cyclohexanecarboxaldehyde or (*E*)-2-butenal as the acceptor, Table 3, entries 1 and 2. Unfortunately, as observed previously with cyclic ketone substrates, the catalyzed reactions with cyclohexanecarboxaldehyde were unsuccessful, with only small amounts (<10%) of the aldol adducts isolated, probably due to competitive enolization. However, when (*E*)-2-butenal was used as the acceptor, the catalyzed reactions proceeded in good yield with 5 mol % of (*S*,*S*)-**1** and (*R*,*R*)-**1** providing 1.3/1 and 6.2/1 syn/anti ratios of the aldol adducts, respectively. Although matched and mismatched cases were again observed, the selectivity in the matched case was somewhat disappointing given the high selectivity observed with benzaldehyde as the acceptor.

As stated above, the uncatalyzed reaction is viewed to proceed though a boatlike closed transition structure with aldehyde coordinated apically to a trigonal bipyramidal silicon center. The low diastereoselectivities make proposals for transition structure arrangements speculative at best. In a simplistic picture, if the oxygenated substituent eclipses the double bond to minimize dipoles then the major product would arise from reaction of the enolate face away from the blocking methyl group (**i**). In the process catalyzed by the chiral phosphoramides, we are still unclear as to the origin of stereoselection with achiral substrates, though we do believe the reactions proceed with aldehyde, enolate, and phosphoramide in a *fac* arrangement about an octahedral silicon center. If a similar eclipsed conformation of the enolate is assumed, then, as a result of the chair−boat flip, the major (now syn) diastereomer is predicted (**ii**). However, in view of the dramatic dependence on the configuration of **1** employed, this is most likely an incomplete analysis.

In conclusion, very high (up to 73/1) syn diastereoselectivity can be obtained in the aldol addition of

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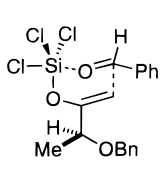
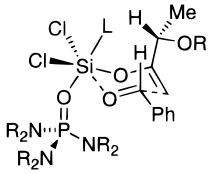


i



ii

α-oxygenated methyl ketone enolates to conjugated aldehydes in the presence of catalytic quantities of a chiral Lewis base. In addition, the trichlorosilyl enolate/phosphoramide technology is compatible with common protecting groups, and isolation and purification of the trichlorosilyl enolates are not necessary when the mercury-catalyzed silyl transfer reaction is used.

Experimental Section

General Methods. See the Supporting Information.

(−)-(*S*)-3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-2-butanone (2a). Methyllithium (1.30 M in Et_2O, 25.4 mL, 33.0 mmol, 1.1 equiv) was added dropwise, via cannula, to a cold (−108 °C, internal) solution of (*S*)-methyl 2-[[dimethyl(1,1-dimethylethyl)silyl]oxy]propanoate[6b] (6.55 g, 30.0 mmol) in THF (90 mL), such that the temperature did not rise above −105 °C (total addition time: 45 min). After the addition, the now cloudy mixture was stirred at −107 °C for 15 min, and then TMSCl (11.4 mL, 90.0 mmol, 3.0 equiv) was added dropwise such that the temperature of the mixture did not rise above −105 °C, 30 min. After the addition of TMSCl was complete, the mixture was stirred at −105 °C for 2 min and then was allowed to warm to room temperature and stir for 25 min, during which time a white precipitate formed. The reaction was quenched by the addition of 1 M aqueous HCl (90 mL), and the resulting mixture was stirred vigorously for 1 h at room temperature, after which time it was neutralized with solid $NaHCO_3$ and the layers were separated. The aqueous phase was extracted with TBME (3 × 50 mL), and the combined organic layers were washed with H_2O (75 mL) followed by brine (75 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, 19/1 hexane/EtOAc) followed by distillation (bulb-to-bulb) to give 4.64 g (76%) of the methyl ketone **2a** as a clear, colorless oil: bp 95 °C ABT (6.0 mmHg); $[\alpha]^{24}_D$ −7.1° (*c* = 2.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.11 (q, *J* = 6.8, 1 H), 2.18 (s, 3 H), 1.27 (d, *J* = 6.8, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 212.74, 75.00, 25.67, 24.79, 20.63, 18.01, −4.79, −5.14; IR (neat) 1721 (s) cm^{-1}; MS (CI) *m*/*z* 231 ($M^+ + 1$, 4), 187 (100); TLC R_f 0.32 (hexane/EtOAc 9/1). Anal. Calcd for $C_{10}H_{22}O_2Si$ (202.37): C, 59.35; H, 10.96. Found: 59.42; H, 10.86.

Data for (−)-(*S*)-1-methyl-2-oxopropyl 2,2-dimethylpropanoate (2b): bp 90 °C ABT (6 mmHg); $[\alpha]^{24}_D$ −24.5° (*c* = 3.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.04 (q, *J* = 7.1, 1 H), 2.15 (s, 3 H), 1.38 (d, *J* = 7.1, 3 H), 1.25 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 206.07, 177.87, 74.74, 38.53, 26.99, 25.60, 15.84; IR (neat) 1728 (s) cm^{-1}; MS (CI) *m*/*z* 173 ($M^+ + 1$, 6), 57 (100); TLC R_f 0.43 (hexane/EtOAc 9/1). Anal. Calcd for $C_9H_{16}O_3$ (172.22): C, 62.77; H, 9.36. Found: C, 62.55; H, 9.32.

Data for (−)-(*S*)-3-(phenylmethoxy)-2-butanone (2c): bp 110 °C ABT (2.0 mmHg); $[\alpha]^{24}_D$ −35.2 ° (*c* = 2.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.29 (m, 5 H), 4.57 (*AB*, *J* = 11.7, 1 H), 4.50 (*AB*, *J* = 11.7, 1 H), 3.91 (q, *J* = 6.9, 1 H), 2.20 (s, 3 H), 1.35 (d, *J* = 6.9, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 211.27, 137.54, 128.50, 127.90, 127.74, 80.82, 71.83, 24.97, 17.26; IR (neat) 1719 (s) cm^{-1}; MS (CI) 179 *m*/*z* ($M^+ + 1$, 3), 91 (100); TLC R_f 0.18 (hexane/EtOAc 9/1). Anal. Calcd for $C_{11}H_{14}O_2$ (178.23): C, 74.13; H, 7.92. Found: C, 74.10; H, 7.89.

(−)-(*S*)-[[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]ethenyl]oxy]trimethylsilane (3a). Ketone **2a** (1.82 g, 9.00 mol) was added dropwise over 10 min to a cold (0 °C) solution of TMSOTf (1.95 mL, 10.8 mmol, 1.2 equiv) and Et_3N (1.88 mL, 13.5 mmol, 1.5 equiv) in benzene (20 mL). During the addition, an oily lower phase appeared. After the addition, the reaction mixture was allowed to stir at 0 °C for 10 min, and then it was warmed to room temperature and stirred for an additional 20 min. The two-phase mixture was then poured into H_2O (20 mL) and extracted with pentane (3 × 20 mL). The organic phases were combined and washed consecutively with H_2O (30 mL), saturated aqueous $CuSO_4$ (2 × 50 mL), H_2O (50 mL), and brine (50 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated to provide an oil that was purified by distillation (bulb-to-bulb) to give 2.33 g (94%) of the silyl enol ether **3a** as a clear, colorless liquid: bp 95 °C ABT (0.3 mmHg); $[\alpha]^{24}_D$ −10.7 ° (*c* = 3.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.41 (s, 1 H), 4.09 (s, 1 H), 4.01 (q, *J* = 6.4, 1 H), 1.24 (d, *J* = 6.4, 3 H), 0.91 (s, 9 H), 0.21 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.90, 87.71, 69.59, 25.83, 22.42, 18.25, 0.13, −4.89, −5.00; IR (neat) 1634 (m) cm^{-1}; MS (CI) *m*/*z* 275 ($M^+ + 1$, 19), 217 (100); TLC R_f 0.66 (hexane/EtOAc 19/1). Anal. Calcd for $C_{13}H_{30}O_2Si_2$ (274.55): C, 56.87; H, 11.01. Found: C, 56.82; H, 11.06.

Data for (−)-(*S*)-1-methyl-2-[(trimethylsilyl)oxy]-2-propenyl 2,2-dimethylpropanoate (3b): bp 85 °C ABT (0.3 mmHg); $[\alpha]^{24}_D$ −21.0° (*c* = 1.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.11 (q, *J* = 6.6, 1 H), 4.30 (s, 1 H), 4.14 (d, *J* = 1.5, 1 H), 1.31 (d, *J* = 6.6, 3 H), 1.21 (s, 9 H), 0.22 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.46, 157.57, 89.48, 70.54, 38.63, 27.09, 18.16, 0.03; IR (neat) 1736 (s), 1641 (s) cm^{-1}; MS (EI) *m*/*z* 244 (M^+, 26), 57 (100); TLC R_f 0.55 (hexane/EtOAc 19/1). Anal. Calcd for $C_{12}H_{24}O_3Si$ (244.41): C, 58.97; H, 9.90. Found: C, 58.81; H, 9.86.

Data for (−)-(*S*)-trimethyl-[[1-[(phenylmethoxy)ethyl]ethenyl]oxy]silane (3c): bp 135 °C ABT (0.35 mmHg); $[\alpha]^{24}_D$ −51.9 ° (*c* = 3.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.26 (m, 5 H), 4.65 (d, *J* = 12.1, 1 H), 4.42 (d, *J* = 12.1, 1 H), 4.36 (d, *J* = 1.1, 1 H), 4.24 (d, *J* = 1.1, 1 H), 3.76 (q, *J* = 6.4, 1 H), 1.31 (d, *J* = 6.4, 3 H), 0.25 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.42, 138.79, 128.30, 127.63, 127.38, 90.22, 76.33, 70.32, 19.53, 0.14; IR (neat) 1633 (s) cm^{-1}; MS (CI) *m*/*z* 251 ($M^+ + 1$, 5), 91 (100); TLC R_f 0.57 (hexane/EtOAc 9/1). Anal. Calcd for $C_{14}H_{22}O_2Si$ (250.41): C, 67.15; H, 8.85. Found: C, 66.95; H, 8.82.

Representative Procedure for Unpromoted Aldol Additions. (1*S*,4*S*)-1-Hydroxy-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1-phenyl-3-pentanone (*anti*-4a) and (1*R*,4*S*)-1-Hydroxy-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1-phenyl-3-pentanone (*syn*-4a). Silyl enol ether **3a** (549 mg, 2.0 mmol) was added dropwise over 1 min to a stirred suspension of $SiCl_4$ (460 μL, 4.0 mmol, 2.0 equiv) and $Hg(OAc)_2$ (1.6 mg, 5 μmol, 0.0025 equiv) in CH_2Cl_2 (2.0 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 1 h and then the volatile components were removed under reduced pressure (0.1 mmHg) to give a cloudy residue. CH_2Cl_2 (2.0 mL) was added, followed by benzaldehyde (203 μL, 2.0 mmol), and the reaction mixture was allowed to stir at room temperature for 9 h. The reaction mixture was then poured into cold (0 °C) saturated aqueous $NaHCO_3$ solution and was stirred for 15 min. The heterogeneous mixture was filtered through Celite, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were combined, dried (Na_2SO_4), filtered, and concentrated to give a crude oil. Purification by column chromatography (SiO_2, hexane/EtOAc 8/1) afforded 503.1 mg (82%) of a mixture of diastereomers **4a** as a clear, colorless oil: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.35−7.20 (m, 5 H, HAr), 2.59 (d, *J* = 4.2), 5.28 (d, *J* = 4.6), 5.04−4.06 (m, 1 H), 4.17 (q, *J* = 6.6), 4.14 (d, *J* = 6.8), 2.96 (dd, *J* = 16.3, 8.6), 2.89 (dd, *J* = 16.3, 8.4), 2.75 (dd, *J* = 16.3, 5.1), 2.61 (dd, *J* = 16.5, 4.6), 1.15 (d, *J* = 6.8), 1.11 (d, *J* = 6.8), 0.83 (s), 0.82 (s), 0.05 (s) 0.02 (s), 0.00 (s); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 210.07, 209.86, 145.51, 145.41, 128.07, 126.93, 126.90, 125.79, 125.75, 74.35, 74.24, 68.50, 68.43, 46.99, 46.60, 25.63, 19.87, 19.71, 17.75, −4.96, −5.04; IR (neat) 1716 (s) cm^{-1}; MS (FAB) 309 *m*/*z* ($M^+ + 1$, 5), 159 (100); TLC R_f 0.44 (hexane/EtOAc 3/1); SFC t_R (1*R*,4*S*)-**4a** 6.39 min (45.2%); t_R (1*S*,4*S*)-**4a** 7.64 min (54.8%) (*R*,*R*-Whelk-01, 1% MeOH in CO_2, 150 bar, 40 °C, 3.0 mL min^{-1}). Anal. Calcd for $C_{17}H_{28}O_3Si$ (308.49): C, 66.19; H, 9.15. Found: C, 65.91; H, 9.03.

Data for (1*S*,4*S*)-1-hydroxy-1-phenyl-4-[(2,2-dimethylpropanoyl)oxy]-3-pentanone (*anti*-4b) and (1*R*,4*S*)-1-hydroxy-1-phenyl-4-[(2,2-dimethylpropanoyl)oxy]-3-pentanone (*syn*-4b): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.35−7.20

(m, 5 H), 5.37 (d, J = 4.9), 5.34 (d, J = 4.6), 5.08−4.96 (m, 2 H), 2.90 (dd, J = 16.4, 9.0), 2.89 (dd, J = 16.4, 8.6), 2.67 (dd, J = 16.1, 4.6), 2.64 (dd, J = 16.1, 3.9), 1.28 (d, J = 7.1), 1.22 (d, J = 6.9), 1.16 (s), 1.16 (s); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 205.36, 205.27, 176.79, 145.19, 145.16, 128.14, 127.01, 125.81, 125.75, 74.45, 74.31, 68.23, 47.73, 47.62, 37.99, 26.76, 15.13, 15.10; IR (neat) 1726 (s) cm^{-1}; MS (CI) 279 m/z (M^+ + 1, 2), 57 (100); TLC R_f 0.36 (hexane/EtOAc 3/1). Anal. Calcd for $C_{16}H_{22}O_4$ (278.35): C, 69.04; H, 7.97. Found: C, 69.12; H, 7.97.

Data for (1*S*,4*S*)-1-hydroxy-1-phenyl-4-(phenylmethoxy)-3-pentanone (*anti*-4c) and (1*R*,4*S*)-1-hydroxy-1-phenyl-4-(phenylmethoxy)-3-pentanone (*syn*-4c): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.36−7.20 (m, 10 H), 5.42 (d, J = 4.6), 5.41 (d, J = 4.9), 5.09−5.01 (m, 1 H), 4.52 (d, J = 11.7), 4.46 (*AB*, J = 11.7), 4.40 (A*B*, J = 11.5), 4.38 (d, J = 11.7), 4.03 (q, J = 7.1), 3.98 (q, J = 7.1), 3.00 (dd, J = 16.1, 9.0), 2.97 (dd, J = 16.1, 8.8), 2.78 (dd, J = 16.1, 4.6), 2.67 (dd, J = 15.9, 4.4), 1.21 (d, J = 6.8), 1.18 (d, J = 7.1); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 209.96, 145.35, 138.14, 128.29, 128.11, 127.67, 127.58, 126.99, 125.83, 125.79, 80.16, 80.01, 70.75, 68.78, 68.53, 47.34, 16.59, 16.42; IR (neat) 1719 (s) cm^{-1}; MS (FAB) m/z 285 (M^+ + 1, 2), 154 (100); TLC R_f 0.21 (hexane/EtOAc 3/1). Anal. Calcd for $C_{18}H_{20}O_3$ (284.38): C, 76.03; H, 7.09. Found: C, 76.03; H, 7.10.

Data for (1*S*,4*S*)-1-cyclohexyl-1-hydroxy-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-3-pentanone (*anti*-5) and (1*R*,4*S*)-1-cyclohexyl-1-hydroxy-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-3-pentanone (*syn*-5): ^{1}H NMR (C_6D_6, 500 MHz) δ 4.02−3.95 (m, 1 H), 3.89−3.82 (m, 1 H), 2.98 (br, OH), 2.70−2.62 (m, 2 H), 1.98−1.85 (m), 1.72−1.55 (m), 1.35−1.28 (m), 1.16 (d, J = 7.0), 1.14 (d, J = 6.8), 1.20−1.02 (m); 0.91 (s), 0.90 (s), −0.02 (s), −0.04 (s), −0.06 (s), −0.06 (s); ^{13}C NMR (C_6D_6, 126 MHz) δ 214.33, 214.25, 75.38, 75.25, 71.60, 43.63, 43.57, 41.44, 41.16, 29.29, 29.22, 28.50, 28.28, 26.84, 26.61, 26.57, 26.50, 26.48, 25.79, 20.46, 20.41, 18.12, −4.80, −5.08; IR (neat) 1714 (s) cm^{-1}; MS (CI) m/z 315 (M^+ + 1, 7), 159 (100); TLC R_f 0.30 (hexane/EtOAc 9/1). Anal. Calcd for $C_{17}H_{34}O_3Si$ (314.54): C, 64.92; H, 10.89. Found: C, 64.83; H, 10.89.

Data for (2*S*,5*S*)-5-hydroxy-2-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-6-octen-3-one (*anti*-6) and (2*S*,5*R*)-5-hydroxy-2-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-6-octen-3-one (*syn*-6): ^{1}H NMR (C_6D_6, 500 MHz) δ 5.68−5.60 (m, 1 H), 5.51−5.45 (m, 1 H), 4.63−4.54 (m, 1 H), 3.98 (d, J = 6.6), 3.95 (q, J = 6.8), 2.79 (dd, J = 17.4, 8.5), 2.78−2.68 (m), 2.67−2.64 (m), 2.60 (dd, J = 17.3, 3.4), 1.50 (br d, J = 6.3, 3 H), 1.12 (d, J = 6.6), 1.11 (d, J = 6.8), 0.89 (s), 0.88 (s), −0.05 (s), −0.06 (s), −0.08 (s); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 210.33, 210.20, 134.82, 134.71, 124.08, 123.98, 74.32, 74.25, 67.00, 66.98, 45.43, 44.86, 25.65, 19.90, 19.79, 17.79, 17.38, −4.89, −5.02; IR (neat) 1719 (s) cm^{-1}; MS (CI) 271 m/z (M^+ + 1, 3), 159 (100); TLC R_f 0.45 (hexane/EtOAc 3/1). Anal. Calcd for $C_{14}H_{28}O_3Si$ (272.46): C, 61.72; H, 10.36. Found: C, 61.53; H, 10.29.

Representative Procedure for Catalyzed Aldol Additions. (1*S*,4*S*)-1-Hydroxy-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1-phenyl-3-pentanone (*anti*-4a) and (1*R*,4*S*)-1-Hydroxy-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1-phenyl-3-pentanone (*syn*-4a). Silyl enol ether **3a** (550.0 mg, 2.0 mmol) was added dropwise over 2 min to a stirred suspension of $SiCl_4$ (460 μL, 4.0 mmol, 2.0 equiv) and $Hg(OAc)_2$ (3.4 mg, 11 μmol, 0.005 equiv) in CH_2Cl_2 (2.0 mL) at room temperature. After complete addition, the reaction mixture was stirred at room temperature for 90 min, and then the volatile components were removed under reduced pressure (0.3 mmHg) to give a cloudy residue. Dichloromethane (2.0 mL) was added, and the mixture was cooled to −76 °C. A solution of (*S*,*S*)-**1** (37.0 mg, 0.1 mmol, 0.05 equiv, dried at 0.1 mmHg for 12 h) in CH_2Cl_2 (1.0 mL) was then added over 1 min via cannula. A solution of benzaldehyde (203 μL, 2.0 mmol) in CH_2Cl_2 (1.0 mL) was then added over 2 min via cannula, and the reaction mixture was stirred at −75 °C for 3 h. The reaction mixture was then rapidly poured into cold (0 °C) saturated aqueous $NaHCO_3$ solution and was stirred for 15 min. The heterogeneous mixture was filtered through Celite, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated to give a crude oil. Purification by column chromatography (SiO_2, hexane/EtOAc 8/1) afforded 525.0 mg (85%) of a mixture of diastereomers **4a** as a clear, colorless oil, SFC: t_R (1*R*,4*S*)-**4a** 5.97 min (60.7%); t_R (1*S*,4*R*)-**4a** 7.18 min (39.3%) (*R*,*R*-Whelk-01, 1% MeOH in CO_2, 150 bar, 40 °C, 3.0 mL min^{-1}).

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Supporting Information Available: Full experimental procedures and characterization data for all compounds described (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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