# Asymmetric Zn-Aldol Reaction of Methyl Vinyl Ketone and Its Synthetic Applications

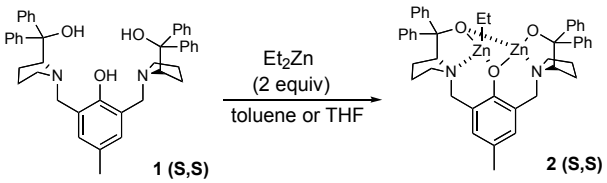
Barry M. Trost*, Seunghoon Shin, Joseph A. Sclafani
*Department of Chemistry, Stanford University, Stanford, California 94305-5080*

## Supporting Information

**General** All reactions were performed under nitrogen atmosphere unless otherwise indicated. Acetone was distilled from Drierite®. Ether and methylene chloride ($CH_2Cl_2$) were purified on an alumina column solvent purification system, and tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Methyl vinyl ketone was purchased from Aldrich and was distilled over anhydrous calcium chloride prior to use. Diethylzinc was purchased from Aldrich (Sure/Seal bottle, either 1.0 M in hexane or 1.1 M in toluene). Standard phenyl ligand (**1**) was synthesized as reported before.[3e]

Flash chromatography was performed with EM Science silica gel (0.040-0.063 mm grade) or 200 mesh Florisil (Aldrich). Analytical thin layer chromatography was performed with 0.2 mm coated commercial silica gel plates (E. Merck, DC Plastifolien, kieselgel 60 F254). Proton and broad-band decoupled $^{13}C$ nuclear magnetic resonance data were acquired on a Varian GEM-300, Mercury-400 or Unity Inova-500 spectrometer as indicated. Chemical shifts are reported in ppm relative to TMS as an internal standard. Infrared (IR) data were recorded in sodium chloride plates on PerkinElmer Paragon 500 FTIR spectrometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. High resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Resource, School of Pharmacy, University of California-San Francisco on a Kratos MS9 spectrometer. All compounds were judged to be pure (>95%) on the basis of 1H NMR except where explicitly indicated otherwise. Proton and carbon NMR spectra are provided in the second Supporting Information document for all new compounds that do not have elemental analysis given.

***Scheme A.*** Generation of Dinuclear Zn Catalyst




**Conditions for Table 1**
**Typical condition (entry 3, Method A, [ald] = 0.3 M, [MVK] = 7 M)**

Under nitrogen atmosphere, benzene (~0.5 mL) was syringed into a test tube capped with rubber septa containing standard phenyl ligand **1** (32 mg, 0.05 mmol). After the tube was immersed in an ice-bath, the tube was carefully connected to a high vacuum (~1 torr) via needle. Then the bath was removed and evaporation was continued until solvent was removed completely. This drying process was repeated once more. To the resulting white solid was added THF (0.5 mL) and then a solution of diethyl zinc (100 μL of 1.0 M soln in hexane, 0.10 mmol) was added dropwise over 5 min at ambient temperature. After being stirred at the same temperature for 20-30 min, a solution of catalyst was obtained (~ 0.1 M in THF).

*Reaction*: Under nitrogen atmosphere, the solution of catalyst prepared as mentioned above was added via syringe to a mixture of freshly distilled (over anhydrous calcium chloride) methyl vinyl ketone (1.0 mL, 12 mmol), isopropanol (0.20 mL, 2.5 mmol), 3-benzyloxy-2,2-dimethylpropionaldehyde (96.1 mg, 0.5 mmol), and 4 A molecular sieve (100 mg) at –78 $^{o}$C. After the addition, the reaction mixture was

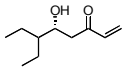
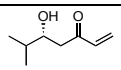
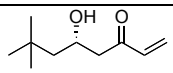
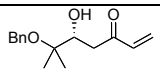
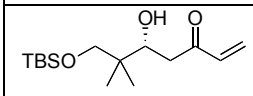
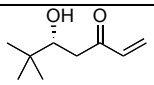
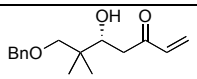
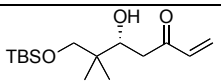
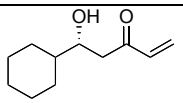
immersed in the cold bath for the amount of time designated. After the reaction, the reaction was quenched with 0.1N HCl (2 mL), and the aqueous phase was extracted with ether (2 mL x 4). The combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure using rotary evaporator with ice-bath. The residue was loaded on a silica gel column (pre-treatred with $Et_3N$) and was eluted with EtOAc/pet = 1/8~1/5 to give 83.7 mg (64 % y) of aldol, 25.6 mg (27 %) of recovered starting material, and 25.6 mg (21 %) of elimination product.

**Typical Condition (entry 9, Method B, [ald] = 0.8 M, [MVK] = 5 M)**

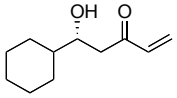
*Catalyst Preparation:*Under nitrogen atmosphere, benzene (~0.5 mL) was syringed into a test tube capped with rubber septa containing standard phenyl ligand (32 mg, 0.05 mmol). After the tube was immersed in an ice-bath, the tube was carefully connected to a high vacuum (~1 torr) via needle. Then the bath was removed and evaporation was continued until solvent was removed completely. This drying process was repeated once more. To the resulting white solid was added anhydrous toluene (0.25 mL), then a solution of diethyl zinc (91 μL of 1.1 M soln in toluene, 0.1 mmol)[1] was added dropwise over 5 min at ambient temperature. After being stirred at the same temperature for 20-30 min, a solution of catalyst was obtained (ca. 0.2 M in toluene).

*Reaction*: Under nitrogen atmosphere, aldehyde (101.2 mg, 0.5 mmol) was syringed into a tube with rubber septa containing freshly distilled (over anhydrous calcium chloride) methyl vinyl ketone (0.25 mL, 3.0 mmol), isopropanol (0.2 mL, 2.5 equiv), and 4 A molecular sieve (100 mg) at room temperature. To the resulting mixture cooled at –78 °C, catalyst solution prepared above was added dropwise over 2 min. The tube was sealed with parafilm and was immersed in the cold bath for the amount of time designated (-15 °C, 14 h). A similar workup procedure and chromatography afforded the aldol product (67.8 mg, 50 %), starting aldehyde (32.5 mg, 32 %), and elimination product (12 %).

***Table A.*** Chiral HPLC Separation Conditions for the Aldol Adducts

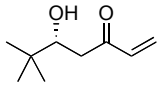
| Compound[a] | Column (Hept/IPA) | |
|---|---|---|
| | Major isomer (min) | Minor isomer (min) |
|  | OD (98/2), 1 mL/min | |
| | 10.2 | 8.5 |
|  | OD (99/1), 1 mL/min | |
| | 23.6 | 17.8 |
|  | OD (99.5/0.5), 1 mL/min | |
| | 18.0 | 16.2 |
|  | OJ (97/7), 1 mL/min | |
| | 14.7 | 17.9 |
|  | AD (99.5/0.5), 0.9 mL/min | |
| | 15.3 | 18.1 |
|  | OJ (99.5/0.5), 1 mL/min | |
| | 8.82 | 10.19 |
|  | OJ (98/2), 1 mL/min | |
| | 20.6 | 22.4 |
|  | OD (99/1), 1 mL/min | |
| | 9.69 | 7.27 |
|  | OD (99.5/0.5), 1 mL/min | |
| | 24.3 | 20.7 |

[a]Absolute stereochemistry was determined by Mandelate method (Trost, B.M. et al. *J.Org.Chem.* **1986**, *51*, 2370)



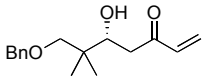
**Entry 1, Table 1**

$^1$H NMR (400 Hz, $CDCl_3$): δ 6.38 (dd, *J* = 10.5, 17.4 Hz, H), 6.25 (dd, *J* = 1.3, 17.3 Hz, H), 5.89 (dd, *J* = 1.1, 11.3 Hz, H), 3.88 (br s, H), 2.97 (d, J = 1.8 Hz, H), 2.78 (dd, *J* = 7.8, 17.0 Hz, H), 2.61 (dd, *J* = 3.8, 16.4 Hz, H), 1.92-0.80 (s, 11H). $^{13}$C NMR (125 Hz, $C_6D_6$): δ 200.8, 136.8, 128.2, 71.5, 43.4, 43.3, 29.2, 28.1, 26.8, 26.5, 26.4, Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95, found C, 72.27; H, 9.47.



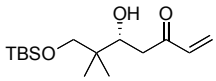
**Entry 2, Table 1**

$[\alpha]_D^{22}$ = +41 (c 0.89 $CHCl_3$). IR (neat): 3501, 2958, 2908, 2872, 1681, 1616, 1480, 1402, 1365, 1295, 1245, 1192, 1171, 1075, 1010, 986, 916 cm$^{-1}$. $^1$H NMR (300 Hz, $CDCl_3$): δ 6.38 (dd, *J* = 10.3, 17.5 Hz, H), 6.25 (dd, *J* = 1.5, 17.5 Hz, H), 5.88 (dd, *J* = 1.2, 10.3 Hz, H), 3.77 (ddd, *J* = 2.0, 3.2, 10.0 Hz, H), 2.93 (d, *J* = 3.4 Hz, H), 2.81 (dd, *J* = 2.0, 17.0 Hz, H), 2.61 (dd, *J* = 10.0, 17.1 Hz, H), 0.83 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 201.9, 136.8, 128.9, 74.8, 41.0, 34.3, 25.7. Chiral HPLC assay: $t_r$ = 15.2 (major), 18.3 (minor) min (Chiralcel AD, λ = 230 nm, heptane : isopropanol = 99/1, 1 mL/min). HRMS calcd for $C_9H_{17}O_2$ [M+H]: 157.1229, found 157.1227.



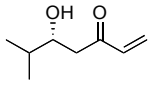
**Entry 3, Table 1**

$[\alpha]_D^{23}$ = +31.4 (c 1.87 $CHCl_3$). IR (neat): 3499, 3089. 3063, 3030, 2963, 2874, 1681, 1615, 1496, 1477, 1454, 1402, 1363, 1308, 1206, 1096, 1027, 988, 917, 738, 698 cm$^{-1}$. $^1$H NMR (500 Hz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 6.38 (dd, *J* = 10.7, 17.6 Hz, H), 6.22 (dd, *J* = 1.0, 17.6 Hz, H), 5.84 (dd, *J* = 1.0, 10.7 Hz, H), 4.50 (ABq, $\nu_A$ = 1.0, $\nu_B$ = 9.3 Hz, 2H), 4.07 (td, *J* = 3.2, 9.3 Hz, H), 3.42 (d, *J* = 3.7 Hz, H), 3.35 (ABq, $\nu_A$ = 9.0, $\nu_B$ = 19.3 Hz, 2H), 2.71 (dd, *J* = 7.3, 16.8 Hz, H), 2.67 (dd, *J* = 3.0, 16.5 Hz, H), 0.97 (s, 3H), 0.92 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 201.1, 138.1, 136.9, 128.6, 128.4, 127.6, 127.5, 78.4, 73.6, 73.5, 41.6, 38.2, 22.1, 19.9. Chiral HPLC assay: $t_r$ = 13.8 (major), 17.8 (minor) min (Chiralcel OJ, λ = 254 nm, heptane : isopropanol = 97/3, 1.0 mL/min). LRMS calcd for $C_{16}H_{23}O_3$: 263.1647, found 263.2.



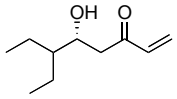
**Entry 4, Table 1**

$[\alpha]_D^{26}$ = +31.1 (c 0.5 $CHCl_3$). $t_r$ = 15.28 (major), 18.08 (minor) min (Chiralcel AD, λ = 230 nm, heptane : isopropanol = 99.5/0.5, 1.0 mL/min). IR (neat): 3500, 2957, 2858, 1682, 1616, 1472, 1403, 1362, 1255, 1095, 990, 837, 764, 668 cm$^{-1}$. $^1$H NMR (400 Hz, $CDCl_3$): δ 6.41 (dd, *J* = 10.5, 17.7 Hz, H), 6.25 (dd, *J* = 1.2, 17.7 Hz, H), 5.84 (dd, *J* = 1.2, 10.2 Hz, H), 4.07 (td, *J* = 3.0, 9.6 Hz, H), 3.65 (d, *J* = 3.0 Hz, H), 3.48 (d, *J* = 1.2 Hz, 2H), 2.76 (dd, *J* = 9.3, 15.6 Hz, H), 2.66 (dd, *J* = 2.5, 15.6 Hz, H), 0.92 (s, 3H), 0.89 (s, 9H), 0.84 (s, 3H), 0.06 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 201.0, 136.9, 128.5, 74.2, 71.9, 41.9, 38.4, 25.8, 21.7, 19.2, 18.1, -5.7. Anal calcd for $C_{15}H_{30}O_3Si$, C: 62.89, H: 10.55, found C: 62.93, H: 11.39.



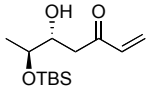
**Entry 5, Table 1**

$[\alpha]_D^{25}$ = +35.7 (c 1.72 $CHCl_3$). IR (neat): 3474, 2963, 1682, 1615, 1470, 1403, 1190, 1085, 1048, 992 cm$^{-1}$. $^1$H NMR (500 Hz, $CDCl_3$): δ 6.35 (dd, *J* = 10.4, 17.7 Hz, H), 6.25 (dd, *J* = 1.0, 17.6 Hz, H), 5.88 (dd, *J* = 1.0, 10.4 Hz, H), 3.85 (td, *J* = 2.7 (d), 6.2 (t) Hz, H), 3.03 (d, *J* = 3.2 Hz, H), 2.77 (d, *J* = 2.4, 17.4 Hz, H), 2.66 (dd, *J* = 9.5, 17.4 Hz, H), 1.76-1.66 (m, H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 201.8, 136.7, 129.1, 72.1, 42.7, 33.0, 18.4, 17.8. Chiral HPLC assay: $t_r$ = 17.8 (minor), 23.6 (major) min (Chiralcel OD, λ = 230 nm, heptane : isopropanol = 99/1, 1.0 mL/min). HRMS calcd for $C_8H_{15}O_2$ [M+H]: 143.1082, found 143.1072.



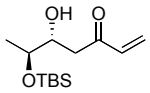
**Entry 6, Table 1**

$[\alpha]_D^{25}$ = +11.1 (c 1.80 $CHCl_3$). IR (neat): 3486, 2963, 2934, 2876, 1681, 1615, 1463, 1402, 1190, 1085, 1030, 989, 963 $cm^{-1}$. $^1H$ NMR (500 Hz, $CDCl_3$): δ 6.36 (dd, *J* = 10.4, 17.6 Hz, H), 6.25 (dd, *J* = 1.0, 17.7 Hz, H), 5.89 (dd, *J* = 1.1, 10.5 Hz, H), 4.12 (m, H), 2.94 (d, *J* = 3.5 Hz, H), 2.77-2.67 (m, 2H), 1.52-1.35 (m, 3H), 1.30-1.20 (m, 2H), 0.93-0.87 (m, 6H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 201.9, 136.7, 129.1, 68.5, 46.0, 42.7, 21.8, 21.4, 11.7, 11.6. Chiral HPLC assay: $t_r$ = 15.9 min (minor), 19.9 min (major) (Chiralcel OD, λ = 230 nm, heptane : isopropanol = 99/1, 1.0 mL/min). HRMS calcd for $C_{10}H_{19}O_2$ [M+H]: 171.1385, found 171.1377.



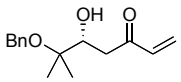
**Entry 7a, Table 1**

$[\alpha]_D^{22}$ = +38.2 (c 1.02 $CHCl_3$). IR (neat): 3480, 2956, 2990, 2895, 2858, 1682, 1616, 1472, 1403, 1257, 1141, 1088, 996, 911, 836, 777 $cm^{-1}$. $^1H$ NMR (500 Hz, $CDCl_3$): δ 6.37 (dd, *J* = 10.6, 17.7 Hz, H), 6.25 (dd, *J* = 0.8, 17.6 Hz, H), 5.89 (dd, *J* = 1.0, 10.6 Hz, H), 3.92 (dddd, *J* = 3.5, 4.0, 5.1, 8.4, H), 3.81 (dq, *J* = 5.1 (d), 6.1 (q) Hz, H), 2.93 (d, *J* = 4.0 Hz, H), 2.83 (dd, *J* = 3.5, 17.1 Hz, H), 2.74 (dd, *J* = 8.4, 17.1 Hz, H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 200.9, 136.9, 129.0, 72.1, 70.8, 41.3, 25.8, 19.0, 18.0, -4.4, -4.8. HRMS calcd for $C_{13}H_{27}O_3Si$ [M+H], 258.1651, found 259.0 (low resolution).



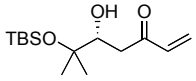
**Entry 7b, Table 1**

$[\alpha]_D^{26}$ = -10.5 (c 1.32 $CHCl_3$). IR (neat): 3481, 2956, 2930, 2896, 2858, 1683, 1616, 1473, 1403, 1256, 11141, 1094, 1005, 996, 836, 771 $cm^{-1}$. $^1H$ NMR (500 Hz, $CDCl_3$): δ 6.38 (dd, *J* = 10.5, 17.6 Hz, H), 6.23 (dd, *J* = 1.1, 17.6 Hz, H), 5.88 (dd, *J* = 1.0, 10.6 Hz, H), 3.94 (m, H), 3.82 (dq, *J* = 4.2(d), 6.2(q) Hz, H), 2.78-2.71 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 200.3, 136.8, 128.9, 71.5, 70.3, 42.1, 25.8, 19.2, 18.0, -4.3, -4.9. Anal Calcd for $C_{13}H_{26}O_3Si$, C:60.42, H:10.14, found C: 60.60, H: 10.12.



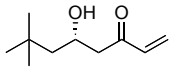
**Entry 8, Table 1**

$[\alpha]_D^{26}$ = +33.7 (c 1.62 $CHCl_3$). $t_r$ = 15.7 (major), 19.7 (minor) min (Chiralcel AD, λ = 230 nm, heptane : isopropanol = 98/2, 1 mL/min). IR (neat): 3490, 3030, 2975, 2360, 1679, 1615, 1497, 1453, 1401, 1147, 1088, 988 $cm^{-1}$. $^1H$ NMR (500 Hz, $CDCl_3$): δ 7.36-7.22 (m, 5H), 6.39 (dd, *J* = 10.6, 17.7 Hz, H), 6.25 (dd, *J* = 1.0, 17.7 Hz, H), 5.87 (dd, *J* = 1.0, 10.6 Hz, H), 4.50 (ABq, $\nu_A$ = 11.4, $\nu_B$ = 22.0 Hz, 2H), 4.10 (ddd, *J* = 2.3, 3.8, 9.6 Hz, H), 3.00 (d, *J* = 3.8 Hz, H), 2.91 (dd, *J* = 2.3, 16.9 Hz, H), 2.76 (dd, *J* = 9.6, 16.8 Hz, H), 1.31 (s, 3H), 1.28 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 201.0, 139.2, 136.8, 129.0, 77.1, 73.3, 63.9, 41.0, 21.8, 20.6. Anal Calcd for $C_{15}H_{20}O_3$, C: 72.55, H: 8.12, found C: 72.48, H: 8.12.



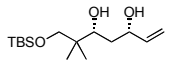
**Entry 9, Table 1**

$[\alpha]_D^{25}$ = +37.5 (c 1.34 $CHCl_3$). $t_r$ = 7.23 (minor), 9.74 (major) min (Chiralcel OD, λ = 230 nm, heptane : isopropanol = 99/1, 1 mL/min). IR (neat): 3508, 2956, 2991, 2888, 2858, 1682, 1617, 1472, 1403, 1363, 1256, 1180, 1154, 1081, 1044, 835, 813, 774 $cm^{-1}$. $^1H$ NMR (400 Hz, $CDCl_3$): δ 6.40 (dd, *J* = 10.5, 17.7 Hz, H), 6.24 (dd, *J* = 1.0, 17.7 Hz, H), 5.88 (dd, *J* = 1.0, 10.5 Hz, H), 3.84 (ddd, *J* = 2.3, 4.3, 9.6 H), 2.85 (dd, *J* = 2.4, 16.5 Hz, H), 2.82 (d, *J* = 4.1 Hz, H), 2.66 (dd, *J* = 9.8, 16.5 Hz, H), 1.25 (s, 3H), 1.23 (s, 3H), 0.86 (s, 9H), 0.12 (s, 3H), 0.12 (s, 3H), $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 201.1, 136.9, 128.9, 75.4, 75.0, 40.9, 26.1, 25.8, 25.0, 18.0, -2.2. Anal. Calc. for $C_{14}H_{28}O_3Si$ C: 61.72, H: 10.36, found C: 61.62, H: 10.16.




**Entry 10, Table 1**

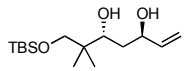
$[\alpha]_D^{26}$ = +31.0 (c 2.25 $CHCl_3$). IR (neat): 3480, 2954, 1682, 1615, 1470, 1403, 1364, 1249, 1203, 1073, 990, 966, 879 $cm^{-1}$. $^1H$ NMR (500 Hz, $CDCl_3$): δ 6.33 (dd, *J* = 10.4, 17.7 Hz, H), 6.23 (dd, *J* = 1.1, 17.7 Hz, H), 5.88 (dd, *J* = 1.1, 10.5 Hz, H), 4.26 (m, H), 2.96 (d, *J* = 2.1 Hz, H), 2.72 (dd, *J* = 25.4, 17.0 Hz, H), 2.71 (dd, *J* = 17.0, 21.0 Hz, H), 1.50 (dd, *J* = 8.7, 14.4 Hz, H), 1.23 (dd, *J* = 2.6, 14.4 Hz, H), 0.96 (s, 9H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 201.5, 136.7, 129.1, 65.3, 49.9, 47.5, 30.3, 30.0. Chiral HPLC assay: $t_r$ = 17.5 (minor), 19.1 (major) min (Chiralcel OD, λ = 230 nm, heptane : isopropanol = 99.5/0.5, 0.9 mL/min). HRMS calcd for $C_{10}H_{18}O_2$: 170.1307, found 170.1299, calcd for $C_6H_{13}O$, [M-$C_4H_5O$]: 101.0966, found 101.0957.




**3a**

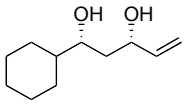
To a solution of 7-t-butyldimethylsiloxy-5-hydroxy-6,6-dimethyl-hept-1-en-3-one (100 mg, 0.349 mmol) in dry tetrahydropyran (3.2 mL) at –78°C was added anhydrous methanol (0.8 mL) and diethylmethoxyborane ($Et_2B(OMe)$, 0.384 mL of 0.1 M THF, 0.384 mmol). The resulting mixture was stirred for 15 min. Sodium borohydride (14.5 mg, 0.384 mmol) was then added portionwise under nitrogen and the mixture was stirred at –78 °C for 3 h. The reaction mixture was quenched with solid Na,K-tartrate (116 mg, 2 equiv) and was diluted with EtOAc and sat. solution of $NaHCO_3$. the mixture was stirred overnight to ensure complete hydrolysis of intermediate boronate ($R_f$ = 0.8, EtOAc:pet = 1/4). The aqueous layer was extracted with EtOAc (2 mL x 3) and the combined organic layers were dried ($MgSO_4$), evaporated, and the residual oil was purified on a silica gel column ($Et_2O$:pet = 1:1) to afford 82.4 mg (82 %) as a single diastereomer.

$[\alpha]_D^{24}$ = +13.8 (c 1.80 $CHCl_3$). IR (neat): 3406, 2957, 2803, 1472, 1362, 1256, 1093, 1007, 922, 837, 776, 669 $cm^{-1}$. $^1H$ NMR (500 Hz, $CDCl_3$): δ 5.87 (ddd, *J* = 5.9, 10.5, 17.1 Hz, H), 5.28 (td, *J* = $1.7^t$, $17.1^d$ Hz, H), 5.07 (td, *J* = $1.5^t$, $10.3^d$ Hz, H), 4.36 (m, H), 4.32 (s br, 2H), 3.78 (dd, *J* = 2.2, 10.7 Hz, H), 3.50 (ABq, $\nu_A$ = 9.8 Hz, $\nu_B$ = 24.7 Hz 2H), 1.62 (td, *J* = $2.6^t$, $14.2^d$, H), 1.54 (ddd, *J* = 9.3, 10.5, 14.0 Hz, H), 0.90 (s, 9H), 0.88 (s, 3H), 0.84 (s, 3H), 0.08 (s, 6H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 140.9, 114.0, 80.6, 73.5, 73.4, 38.0, 37.9, 25.7, 22.2, 19.0, 18.0, -5.7. LRMS calcd for [M+H] $C_{15}H_{33}O_3Si$, 289.2, found 289.4.



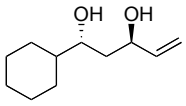

**3b**

To a flask containing tetramethylammonium triacetoxyborohydride ($Me_4NBH(OAc)_3$ (490 mg, 1.86 mmol) was added acetonitrile (2 mL) and AcOH (1 mL) and the mixture was stirred at ambient temperature for 30 min. After cooling the mixture to –25 °C, the 7-(tert-butyldimethylsilyloxy)-5-hydroxy-6,6-dimethyl-hept-1-en-3-one (66.6 mg, 0.232 mmol) in acetonitrile (1.0 mL) was added and the mixture was stirred for 12 h at –25 °C. The mixture was quenched with a saturated solution of Na,K-tartrate and was diluted with dichloromethane (2 mL), then the mixture was neutralized to pH 7 using 2 N NaOH solution. After stirring 3 h, the phase was separated and the aqueous phase was extracted with dichloromethane (3 mL x 5). The combined organic layers were dried ($MgSO_4$) and evaporated and the resulting oil was purified on silica gel chromatography ($Et_2O$:pet = 1:2) to afford 55.5 mg (83 %) of colorless oil. The *anti/syn* ratio was determined to be 90/10, as judged from $^1H$ NMR. $[\alpha]_D^{24}$ = +0.43 (c 1.10 $CHCl_3$). IR (neat): 3411, 2952, 2811, 1470, 1362, 1054, 1005, 937 $cm^{-1}$. $^1H$ NMR (500 Hz, $CDCl_3$): δ 5.94 (ddd, *J* = 5.1, 10.5, 17.2 Hz, H), 5.32 (td, *J* = $1.7^t$, $17.2^d$ Hz, H), 5.13 (td, *J* = $1.7^t$, $10.5^d$ Hz, H), 4.47 (m, H), 4.13 (dd, *J* = 1.2, 3.5 Hz, H), 3.83 (ddd, *J* = 2.1, 3.6, 11.0 Hz, H), 3.50 (ABq, $\nu_A$ = 9.7 Hz, $\nu_B$ = 13.8 Hz, 2H), 3.18 (d, *J* = 6.5 Hz, H), 1.73 (ddd, *J* = 3.4, 11.1, 14.1 Hz, H), 1.57 (dd br, *J* = 6.8, 14.0 Hz, H), 0.89 (s, 9H), 0.87 (s, 3H), 0.81 (s, 3H), 0.07 (s, 6H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 141.1, 113.9, 76.3, 73.6, 70.4, 37.8, 37.1, 25.8, 22.2, 18.9, 18.0, -5.71, -5.74. LRMS calcd for [M+H] $C_{15}H_{33}O_3Si$, 289.2, found 289.4.



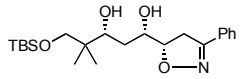
**3c**

A similar procedure was followed as described in the preparation of **3a** (72 % yield as a single diastereomer). $[\alpha]_D^{24}$ = +7.85 (c 2.88 $CHCl_3$). IR (neat): 3356, 2925, 2853, 1450, 1317, 1064, 990, 922, 893, 850 $cm^{-1}$. $^1H$ NMR (400 Hz, $CDCl_3$): δ 5.84 (ddd, *J* = 6.0, 10.4, 17.2 Hz, H), 5.22 (td, *J* = $1.5^t$, $17.2^d$ Hz, H), 5.05 (td, *J* = $1.4^t$, $10.4^d$ Hz, H), 4.29 (m, H), 3.62 (dd br, *J* = 5.0, 8.5 Hz, H), 3.40 (s, H), 3.04 (s, H), 1.79-1.68 (m, 3H), 1.68-1.58 (m, 3H), 1.58-1.47 (m, H), 1.35-1.22 (m, H), 1.22-1.09 (m, 3H), 1.09-0.88 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 140.7, 114.3, 76.8, 74.0, 44.2, 39.6, 28.6, 27.9, 26.4, 26.2, 26.2. LRMS calcd for [M+H] 185.1542, found 185.2.



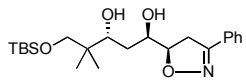
**3d**

A similar procedure was followed as described in the preparation of **3a** (81 % yield of a mixture of diastereomers, anti/syn = 91/9). $[\alpha]_D^{24}$ = -0.39 (c 1.28 $CHCl_3$). IR (neat): 3363, 2926, 2853, 1450, 1416, 1062, 1039, 991, 921, 832 $cm^{-1}$. $^1H$ NMR (500 Hz, $CDCl_3$): δ 5.89 (ddd, *J* = 5.2, 10.5, 17.2 Hz, H), 5.26 (td, *J* = $1.6^t$, $17.2^d$ Hz, H), 5.10 (td, *J* = $1.5^t$, $10.5^d$ Hz, H), 4.43 (m, H), 3.64 (ddd, *J* = 2.4, 6.2, 8.9 Hz, H), 3.30 (s br, H), 2.83 (s br, H), 1.86-1.80 (m, H), 1.78-1.68 (m, 3H), 1.68-1.58 (m, 3H), 1.36-1.28 (m, H), 1.28-1.04 (m, 3H), 1.04-0.80 (m, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 140.7, 114.1, 73.0, 70.4, 43.6, 39.1, 28.8, 28.2, 26.4, 26.1, 26.0.



**Entry 1, Table 2**

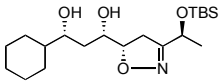
To a solution of starting diol **3a** (24.1 mg, 0.0835 mmol, dried azeotropically over benzene) in dichloromethane (0.5 mL) at –78 °C was added ethylmagnesium bromide (250 μL of 1.0 M soln in THF, 0.250 mmol) and stirred at this temperature for 20 min. In a separate flask, a solution of benzohydroximoyl chloride (19.4 mg, 0.125 mmol) and isopropanol (19.2 μL, 0.25 mmol) in dichloromethane (0.5 mL) at –78 °C was treated dropwise with ethylmagnesium bromide(84 μL of 1.0 M soln in THF, 0.084 mmol). The solution of magnesium alkoxide prepared above was cannulated into the solution of nitrile oxide at –78 °C, stirred 30 min, and kept at –25 °C for 10 h. The reaction was quenched with half saturated $NH_4Cl$ (aq. soln) and extracted with $CH_2Cl_2$ (2 mL x 4). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The residue was separated on a silica gel chromatography (EtOAc/Pet = 1/1) to give 20.0 mg (59 %) of 2-isoxalozine product as colorless oil. $[\alpha]_D^{24}$ = +98.9 (c 1.80 $CHCl_3$). IR (neat): 3443, 2956, 2929, 2857, 1472, 1447, 1359, 1254, 1091, 910, 837 $cm^{-1}$. $^1H$ NMR (400 Hz, $CDCl_3$): δ 7.70-7.65 (m, 2H), 7.43-7.38 (m, 3H), 4.82 (ddd, *J* = 3.8, 8.1, 10.1 Hz, H), 4.42 (d, *J* = 2.9 Hz, H), 4.18 (d, *J* = 2.0 Hz, H), 4.05 (m, H), 3.79 (td, *J* = 3.0, 10.1 Hz, H), 3.49 (ABq, $\nu_A$ = 9.8, $\nu_B$ = 15.4 Hz, 2H), 3.42 (dd, *J* = 8.1, 16.8 Hz, H), 3.34 (dd, *J* = 11.0, 16.8 Hz, H), 1.73-1.61 (m, 2H), 0.89 (s, 9H), 0.88 (s, 3H), 0.84 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 156.8, 130.0, 129.5, 128.6, 126.7, 82.8, 80.3, 73.5, 72.7, 38.1, 36.0, 32.4, 25.7, 22.2, 18.9, 18.0, -5.7. Anal calcd for $C_{22}H_{37}NO_4Si$, C: 64.82, H: 9.15, N: 3.44, found C: 65.00, H: 8.91, N: 3.29.



**Entry 2, Table 2**

A procedure described for the preparation **Entry 3, Table 2** was similarly followed to give 71 % of product as colorless oil. $[\alpha]_D^{24}$ = -61.5 (c 2.1 $CHCl_3$). IR (neat): 3447, 2956, 2929, 2857, 1472, 1447, 1393, 1359, 1254, 1077, 1006, 938, 910, 836 $cm^{-1}$. $^1H$ NMR (400 Hz, $CDCl_3$): δ 7.70-7.62 (m, 2H), 7.42-7.35 (m, 3H), 4.68 (ddd, *J* = 4.3, 8.2, 12.7 Hz, H), 4.04 (s br, H), 3.98 (d, *J* = 7.6 Hz, H), 3.87 (d, *J* = 10.7 Hz, H), 3.51 (ABq, $\nu_A$ = 9.8, $\nu_B$ = 16.5 Hz, 2H), 3.39 (dd, *J* = 10.7, 16.6 Hz, H), 3.32 (dd, *J* = 8.4, 16.6 Hz, H), 2.31 (s br, H), 1.73 (ddd, *J* = 1.6, 10.1, 13.9 Hz, H), 1.55 (ddd, *J* = 2.5, 11.0, 13.6 Hz, H), 0.92 (s,

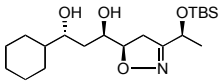
3H), 0.90 (s, 9H), 0.84 (s, 3H), 0.079, 0.078 (s, 3H each). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 157.1, 130.1, 129.3, 128.6, 126.7, 84.4, 75.4, 73.9, 69.8, 37.8, 37.3, 35.9, 25.8, 22.3, 18.5, 18.1, -5.7, -5.8. Anal calcd for $C_{22}H_{37}NO_4Si$, C: 64.82, H: 9.15, N: 3.44, found C: 64.94, H: 9.21, N: 3.49.




**Entry 3, Table 2**

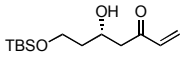
**Representative procedure:** A solution of oxime corresponding to **4b** (61.0 mg, 0.300 mmol) was treated with $^t$BuOCl (32.6 mg, 3.00 mmol) in dichloromethane (1.0 mL) for 30 min at –78 $^o$C. In a separate flask, a mixture of *cis*-diol **3c** (36.8 mg, 0.200 mmol) and isopropanol (45.9 μL, 0.60 mmol) in dichloromethane (1.0 mL) was treated with ethylmagnesium bromide (600μL, 1.0 M in THF, 0.60 mmol) at –78 $^o$C and stirred for 10 min. The solution of nitrile oxide solution formed above was transferred into this mixture dropwise at rt. After 8 h at rt, the mixture was treated with half saturated $NH_4Cl$ (aq. soln) and extracted with $CH_2Cl_2$ (2 mL x 4). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated *in vacuo*. The residue was separated on a silica gel chromatography (EtOAc/Pet = 1/1) to give 53.4 mg (69 %) of dihydroisoxazole as colorless oil.

$[\alpha]_D^{24}$ = +19.6 (c 1.31 $CHCl_3$). IR (neat): 3384, 2926, 1674, 1634, 1558, 1455, 1258, 1218, 1093, 953, 834, 778 cm$^{-1}$. $^1$H NMR (400 Hz, $CDCl_3$): δ 4.71 (q, *J* = 7.1 Hz, H), 4.50 (ddd, *J* = 5.5, 7.1, 10.8 Hz, H), 3.78 (ddd, *J* = 3.2, 5.5, 9.3 Hz, H), 3.63 (ddd, *J* = 2.6, 5.4, 7.9 Hz, H), 3.05 (dd, *J* = 10.8, 17.4 Hz, H), 2.89 (dd, *J* = 7.3, 17.5 Hz, H), 1.82-1.70 (m, 3H), 1.70-1.62 (m, 3H), 1.62-1.52 (m, H), 1.34 (d, *J* = 6.7 Hz, 3H), 1.28-1.08 (m, 4H), 1.08-0.92 (m, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 162.4, 82.5, 76.5, 73.7, 64.8, 44.1, 35.1, 34.6, 28.7, 27.8, 26.4, 26.2, 26.1, 25.6, 22.1, 18.0, -4.8, -5.0. Anal calcd for $C_{20}H_{39}NO_4Si$, C: 62.29, H: 10.19, N: 3.63, found C: 62.35, H: 10.24, N: 3.65.



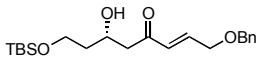

**Entry 4, Table 2**

A similar procedure to the one for the preparation of **Entry 1, Table 2** was followed. (60 % yield (87 % brsm, estimated from the inseparable mixture of starting material and the desired product, in a molar ratio of 33:67. The yield is based on the estimation from NMR spectra of mixture.) IR (neat): 3396, 2928, 2854, 1635, 1372, 1337, 1258, 1093, 1028, 952, 877, 834, 778 cm$^{-1}$. $^1$H NMR (500 Hz, $CDCl_3$): δ 4.72 (q, *J* = 6.5 Hz, H), 4.47 (ddd, *J* = 4.9, 7.8, 12.8 Hz, H), 3.83 (m, H), 3.68 (m, H), 3.05 (dd, *J* = 10.7, 17.2 Hz, H), 2.90 (dd, *J* = 7.9, 17.2 Hz, H), 2.52 (d, *J* = 6.4 Hz, H), 2.14 (d, *J* = 5.0 Hz, H), 1.80-1.70 (m, 3H), 1.70-1.60 (m, 3H), 1.56 (ddd, *J* = 2.7, 5.6, 12.5 Hz, H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.30-1.10 (m, 4H), 1.10-0.93 (m, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 163.0, 83.3, 72.8, 70.6, 44.0, 37.1, 35.5, 29.2, 28.5, 26.7, 26.4, 26.3, 25.9, 22.6, 18.2, -4.6, -4.7. Anal calcd for $C_{20}H_{39}NO_4Si$, C: 62.29, H: 10.19, N: 3.63, found C: 62.25, H: 10.16, N: 3.42.




**5**

$^1$H NMR (400 Hz, $CDCl_3$): δ 6.37 (dd, *J* = 10.4, 17.7 Hz, H), 6.25 (dd, *J* = 1.1, 17.7 Hz, H), 5.89 (dd, *J* = 1.1, 10.4 Hz, H), 4.15 (m, H), 3.63 (dd, *J* = 5.0, 10.0 Hz, H), 3.58 (dd, *J* = 5.1, 10.1 Hz, H), 2.94 (d, *J* = 4.4 Hz, H), 2.79 (d, *J* = 6.1 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), $^{13}$C NMR (100 MHz, $CDCl_3$): δ 200.2, 136.8, 129.1, 68.3, 66.2, 42.2, 25.8, 18.2, -5.41, -5.43.




**6**

To a solution of Grubbs (II) catalyst (4.0 mg, 4.68 μmol) in $CH_2Cl_2$ (0.5 mL) was added allyl benzylether (41.7 mg, 0.274 mmol), followed by portionwise addition of vinyl ketone **5** (22.9 mg, 0.0937 mmol) in $CH_2Cl_2$ (0.5 mL). The resulting solution was stirred under reflux for 4 h. The residue was directly loaded onto a silica gel column and eluted with EtOAc/pet = 1/4 to give 15.9 mg (65 %) of **6** as pale brown oil. $^1$H NMR (500 Hz, $CDCl_3$): δ 7.40-7.35 (m, 5H), 6.87 (td, *J* = 4.3$^t$, 16.0$^d$ Hz, H), 6.42 (td, *J* = 2.1$^t$, 16.0$^d$ Hz, H), 4.57 (s, 2H), 4.21 (s, 2H), 4.14 (quintet, *J* = 5.8 Hz, H), 3.63 (dd, *J* = 5.1 Hz, H), 3.57 (dd, *J* = 5.9, 10.0 Hz, H), 2.77 (d, *J* = 5.9 Hz, 2H), 0.90 (s, 9H), 0.070 (s, 3H), 0.066 (s, 3H). $^{13}$C NMR (125 MHz,

$CDCl_3$): δ 199.8, 143.4, 137.8, 129.8, 128.8, 128.2, 128.0, 73.2, 69.0, 68.6, 66.5, 43.5, 26.1, 18.5, -5.1.HRMS calcd for $C_{20}H_{32}O_4Si$ [M+H], 365.2148, found 365.2139.