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The Chemistry of Trichlorosilyl Enolates. 6. Mechanistic Duality in the Lewis Base-Catalyzed Aldol Addition Reaction

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SUPPORTING INFORMATION

General Experimental

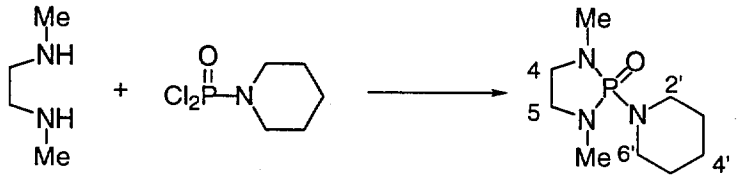
^{1}H NMR, ^{13}C NMR ^{19}F NMR, ^{31}P NMR spectra were recorded on a Varian Unity 400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) or a Varian Unity 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) spectrometer. Spectra were referenced to residual chloroform (δ 7.26 ppm for ^{1}H) in deuteriochloroform and deuteriochloroform itself (δ 77.0 ppm for ^{13}C). ^{31}P NMR spectra were recorded on a Unity 400 (162 MHz) using 85% phosphoric acid as an external reference (δ 0.00 ppm). Chemical shifts and coupling constants are reported in ppm (δ) and in Hz, respectively. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sext (sextet), sept (septet), and m (multiplet). Mass spectroscopy was performed by the University of Illinois Mass Spectrometry Center. Electron impact (EI) spectra were performed on a Finnigan-MAT CH-spectrometer and chemical ionization (CI) spectra were obtained on a VG 70-VSE spectrometer using *i*-butane or methane as the carrier gas. Data are reported in the form of *m/z* (intensity relative to base peak=100). Infrared spectra (IR) were recorded on a Mattson Galaxy 5020 spectrophotometer. Peaks are reported in cm^{-1} with relative intensities indicated by s (strong, 67-100%), m (medium, 34-66%), and w (weak, 0-33%). Optical rotations were obtained on a JASCO DIP-360 digital polarimeter. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Analytical thin layer chromatography was performed on Merck silica gel plates with QF-254 indicator visualized by UV light, iodine, phosphomolybdic acid, anisaldehyde and/or

potassium permanganate. Diethyl ether and isopropyl alcohol were of reagent grade and used as received. Other solvents for extraction and chromatography were of technical grade and used after distillation from the indicated drying agents; hexane and dichloromethane ($CaCl_2$); ethyl acetate (K_2CO_3). Dry solvents were prepared by distillation from the indicated drying agents under nitrogen; dichloromethane (P_4O_{10}); diethyl ether and tetrahydrofuran (THF) (sodium benzophenone ketyl); hexane (sodium). Column chromatography was performed using EM Science 230-400 mesh silica gel. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1090 Series II Liquid Chromatography with a photometric detector (254 nm). CSP HPLC analyses were performed using a DAICEL ChiralCel OJ or AD column.

Melting points were obtained on a Thomas-Hoover apparatus. In Kugelrohr distillation (Buchi GKR-50 Kugelrohr) boiling points were of air-bath temperatures.

1,3-Dimethyl-2-piperidino-1,3,2-diazaphospholidine 2-Oxide (5a)



5a

To a solution of triethylamine (2.3 mL, 17 mmol, 2.5 equiv) in 150 mL of dry CH_2Cl_2 at reflux under nitrogen was added *N,N'*-dimethylethylenediamine (0.71 mL, 6.7 mmol, 1.0 equiv) in 30 mL of dry CH_2Cl_2 and piperidinophosphorus dichloride[1] (1.02 mL, 6.7 mmol) in 30 mL of dry CH_2Cl_2 simultaneously over 2 h using a syringe pump. The solution was heated to reflux for 40 h then was condensed under reduced pressure to give a colorless residue, which was purified by column chromatography on silica gel (ethyl acetate, ethyl acetate/2-propanol, 9/1, and then ethyl acetate/2-propanol, 7/3 as eluents) and distillation (bp 120-125°C/0.05 mmHg; Kugelrohr) to give

1.45 g (quant.) of **5a** as hygroscopic crystals. Analytical sample was prepared by further recrystallization from hexane.

Analytical Data for **5a**:

mp: 55-56°C (hexane)

^{1}H NMR: (400 MHz, $CDCl_3$)

3.11 (m, 2H, C(4/5)H_2), 3.05-2.96 (m, 6H, C(4/5)H_2, C(2', 6')H_2), 2.49 (d, J = 9.8, 6H, CH_3), 1.51 (m, 2H, C(4')H_2), 1.41 (m, 4H, C(3', 5')H_2).

^{13}C NMR: (100 MHz, $CDCl_3$)

47.2 (d, J = 12.2, C(4, 5)), 45.3 (d, J = 3.1, C(2', 6')), 31.5 (d, J = 4.6, CH_3), 26.7 (d, J = 3.8, C(3', 5')), 24.7 (C(4')).

^{31}P NMR: (162 MHz, $CDCl_3$)

26.44

IR: ($CHCl_3$)

2979 (m), 2938 (s), 2852 (m), 1493 (w), 1482 (w), 1470 (w), 1445 (w), 1376 (w), 1351 (w), 1338 (w), 1264 (m), 1230 (m), 1191 (m), 1166 (s), 1122 (w), 1068 (m), 1040 (m), 1026 (w), 961 (s), 943 (m), 863 (w), 853 (w), 834 (w), 670 (w), 665 (w), 547 (w)

MS: (EI, 70 eV)

217 (M^+, 30), 133 (44), 131 (8), 90 (8), 85 (11), 84 (100)

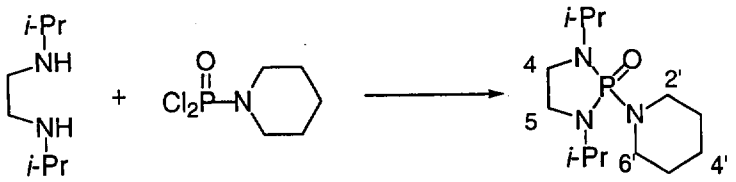
TLC: Rf 0.20 (EtOAc/*i*-PrOH, 9/1)

Anal.: $C_9H_{20}N_3OP$ (217.25)

Calcd.: C, 49.76; H, 9.28; N, 19.34; P, 14.26.

Found: C, 49.56; H, 9.22; N, 19.46; P, 14.34.

1,3-Diisopropyl-2-piperidino-1,3,2-diazaphospholidine 2-Oxide (5b)



5b

To a solution of triethylamine (2.4 mL, 17.5 mmol, 2.5 equiv) in 150 mL of dry CH_2Cl_2 at reflux under nitrogen was added *N,N'*-diisopropylethylenediamine (1.27 mL, 7.0 mmol, 1.0 equiv) in 30 mL of dry CH_2Cl_2 and piperidinophosphorus dichloride (1.07 mL, 7.0 mmol) in 30 mL of dry CH_2Cl_2 simultaneously over 2 h using a syringe pump. The solution was heated to reflux for 36 h then concentrated under reduced pressure to give a colorless residue, which was purified by column chromatography on silica gel (ethyl acetate, ethyl acetate/2-propanol, 19/1 then ethyl acetate/2-propanol, 9/1 as eluents) and distillation (bp 145°C/0.05 mmHg; Kugelrohr) to give hygroscopic colorless crystals. Analytical sample was prepared by further recrystallization from hexane to afford 0.949 g (50% yield) of **5b**.

Analytical Data for **5b**:

mp: 52-53°C (hexane)

^{1}H NMR: (400 MHz, $CDCl_3$)

3.34 (d sept, J = 8.2 Hz, 6.6, 2H, CH), 3.09 (m, 2H, C(4/5)H_2), 2.97 (m, 6H, C(4/5)H_2, C(2', 6')H_2), 1.49 (m, 2H, C(4')H_2), 1.41 (m, 4H, C(3' 5')H_2), 1.13 (d, J = 6.6 Hz, 6H, CH_3), 1.08 (d, J = 6.6 Hz, 6H, CH_3).

^{13}C NMR: (100 MHz, $CDCl_3$)

45.6 (d, J = 3.1, C(2', 6')), 44.1 (d, J = 5.3, CH), 39.0 (d, J = 13.0, C(4, 5)), 26.7 (d, J = 4.6, C(3', 5')), 24.8 (C(4')), 21.4 (d, J =2.3, CH_3), 21.2 (d, J = 4.6, CH_3).

^{31}P NMR: (162 MHz, $CDCl_3$)

22.44

IR: ($CDCl_3$)

2970 (s), 2937 (s), 2851 (m), 1477 (w), 1464 (w), 1452 (w), 1443 (w), 1401 (w), 1390 (w), 1365 (w), 1336 (w), 1230 (m), 1222 (m), 1212 (m), 1179 (s), 1167 (m), 1112 (m), 1064 (m), 1027 (w), 960 (s), 862 (w), 698 (w), 669 (w), 561 (w)

MS: (EI, 70 eV)

273 (M^+, 34), 259 (10), 258 (70), 189 (15), 175 (79), 147 (8), 133 (17), 105 (17), 85 (10), 84 (100), 72 (12)

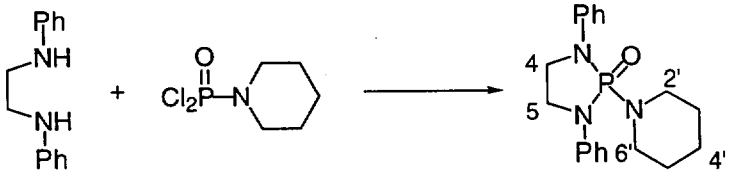
TLC: R_f 0.71 (EtOAc/*i*-PrOH, 9/1)

Anal.: $C_{13}H_{28}N_3OP$ (273.36)

Calcd.: C, 57.12; H, 10.32; N, 15.37; P, 11.33.

Found: C, 56.82; H, 10.46; N, 15.56; P, 11.21.

1,3-Diphenyl-2-piperidino-1,3,2-diazaphospholidine 2-Oxide (5c)



5c

To a solution of *N,N'*-diphenylethylenediamine (2.12 g, 10 mmol, 1.0 equiv) in 20 mL of dry 1,2-dichloroethane were added triethylamine (3.5 mL, 25 mmol, 2.5 equiv) and piperidinophosphorus dichloride (1.53 mL, 10 mmol) at rt under nitrogen. The reaction mixture was heated to reflux for 19 h whereupon the contents of the flask solidified. The solid mass was filtered with help of CH_2Cl_2 and was washed with CH_2Cl_2. The filtrate and the washings were combined and concentrated under reduced pressure to give tan solid, which was purified by column chromatography on silica gel (CH_2Cl_2 then CH_2Cl_2/2-propanol, 20/1 as eluents) and recrystallization from benzene/hexane to afford 1.74 g (51 % yield) of **5c** as colorless fine needles.

Analytical Data for **5c**:

mp: 169-171°C (benzene-hexane)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.33 (t, J = 7.9, 4H, *m*-Ph), 7.17 (d, J = 7.9 Hz, 4H, *o*-Ph), 7.00 (t, J = 7.3 Hz, 2H, *p*-Ph), 3.81 (m, 4H, C(4, 5)H_2), 3.08 (m, 4H, C(2', 6')H_2), 1.40 (m, 2H, C(4')H_2), 1.26 (m, 4H, C(3', 5')H_2).

^{13}C NMR: (125 MHz, $CDCl_3$)

141.7 (d, J = 7.4 Hz, *ipso*-Ph), 129.2 (*m*-Ph), 121.3 (*p*-Ph), 116.2 (d, J = 4.6 Hz, *o*-Ph), 45.0 (d, J = 2.8 Hz, C(2', 6')), 42.5 (d, J = 11.0 Hz, C(4, 5)), 25.5 (d, J = 4.6 Hz, C(3', 5')), 24.3 (C(4')).

^{31}P NMR: (162 MHz, $CDCl_3$)

13.32.

IR: (KBr)

2950 (m), 2933 (s), 2873 (m), 2853 (m), 2836 (s), 1598 (s), 1491 (s), 1465 (m), 1452 (m), 1438 (m), 1400 (m), 1383 (s), 1342 (s), 1325 (m), 1286 (s), 1249 (s), 1219 (s), 1187 (s), 1166 (s), 1147 (m), 1121 (s), 1072 (s), 1033 (s), 997 (s), 962 (s), 863 (m), 831 (m), 754 (s), 737 (m), 708 (s), 691 (s), 591 (m), 526 (s)

MS: (EI, 70 eV)

342 (M^++1, 22), 341 (M^+, 91), 258 (58), 257 (34), 153 (23), 152 (32), 119 (36), 107 (10), 106 (100), 105 (41), 104 (30), 84 (89), 77 (28).

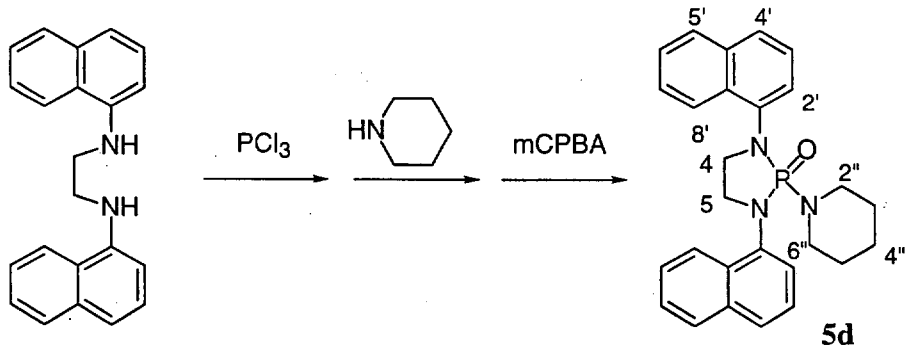
TLC: Rf 0.83 (EtOAc)

Anal.: $C_{19}H_{24}N_3OP$ (341.39)

Calcd.: C, 66.85; H, 7.09; N, 12.31; P, 9.07.

Found: C, 66.66; H, 7.04; N, 12.19; P, 8.88.

1,3-Di-(1-naphthyl)-2-piperidino-1,3,2-diazaphospholidine 2-Oxide (5d)



5d

To a stirred cold (-78°C) solution of PCl_3 (0.61 mL, 7.0 mmol, 1.1 equiv) in 10 mL of dry CH_2Cl_2 was added 1,2-di-(1-naphthylamino)ethane[2] (2.0 g, 6.4 mmol) in 10 mL of dry CH_2Cl_2 through a dropping funnel under nitrogen. Then triethylamine (2.2 mL, 16 mmol, 2.5 equiv) was added at the same temperature. The mixture was warmed to rt and stirred for 24 h. After filtration of the precipitates, the filtrate was condensed under reduced pressure to remove the excess reagents (PCl_3 and triethylamine).

To a stirred suspension of residue in 13 mL of dry CH_2Cl_2 was added piperidine (2.3 mL; 2.3 mmol) at rt. The mixture was stirred for 20 h, filtered to remove the precipitates, and condensed under reduced pressure to remove excess piperidine.

The residue was dissolved in 10 mL of CH_2Cl_2. *m*-Chloroperoxybenzoic acid (50%, 2.21g, 6.4 mmol) in 10 mL of CH_2Cl_2 was added dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 h. Then saturated aqueous $NaHCO_3$ was added with stirring. The aqueous layer was separated and extracted with CH_2Cl_2 twice. The combined organic solutions were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated to give a crude material, which was purified by chromatography (silica gel, benzene then benzene/ethyl acetate, 4/1 as eluents) and recrystallized from diethyl ether/hexane to give 1.29 g (46% yield) of **5d** as slightly tan crystals.

Analytical Data for **5d**:

mp: 170-171°C (CH_2Cl_2-hexane)

^{1}H NMR: (500 MHz, $CDCl_3$)

8.44 (d, J = 8.4, 2H, C(8')H), 7.93 (d, J = 7.3, 2H, C(2'/4')H), 7.91 (d, J = 8.1, 2H, C(5')H), 7.77 (d, J = 8.2, 2H, C(2'/4')H), 7.60 (ddd, J = 8.4, 6.8, 1.3, 2H, C(7')H), 7.53 (ddd, J = 8.2, 7.0, 1.1, 2H, C(6')H), 7.50 (t, J = 7.9, 2H, C(3')H), 4.19 (m, 2H, C(4/5)H_2), 3.82 (m, 2H, C(4/5)H_2), 3.06 (m, 4H, C(2", 6")H_2), 1.14 (m, 2H, C(4")H_2), 0.92 (m, 4H, C(3", 5")H_2).

^{13}C NMR: (100 MHz, $CDCl_3$)

138.0 (d, J = 4.6), 134.8, 131.3 (d, J = 5.3), 128.5, 126.6, 126.1, 126.0, 125.9, 124.5 (d, J = 3.0), 123.5 (br), 49.3 (d, J = 12.2, C(4, 5)), 45.7 (d, J = 3.1, C(2", 6")), 26.0 (d, J = 4.6, C(3", 5")), 24.1 (C(4")).

^{31}P NMR: (162 MHz, $CDCl_3$)

16.56.

IR: (KBr)

3037 (w), 3010 (w), 2964 (m), 2931 (s), 2846 (s), 1591 (s), 1574 (s), 1509 (m), 1478 (w), 1462 (s), 1441 (m), 1394 (s), 1372 (s), 1341 (s), 1276 (s), 1237 (s), 1219 (s), 1205 (s), 1180 (s), 1168 (s), 1116 (s), 1100 (s), 1080 (s), 1071 (s), 1028 (s), 1017 (m), 966 (s), 936 (m), 804 (s), 797 (s), 775 (s), 731 (s), 680 (m), 646 (m), 623 (m), 605 (w),

MS: (EI, 70 eV)

442 (M^++1, 51), 441 (M^+, 100), 359 (25), 358 (77), 357 (18), 291 (33), 272 (16), 203 (20), 188 (16), 186 (18), 170 (11), 169 (32), 168 (18), 167 (11), 157 (21), 156 (92), 155 (40), 154 (51), 143 (10), 130 (10), 129 (15), 128 (23), 127 (28), 115 (18), 84 (35).

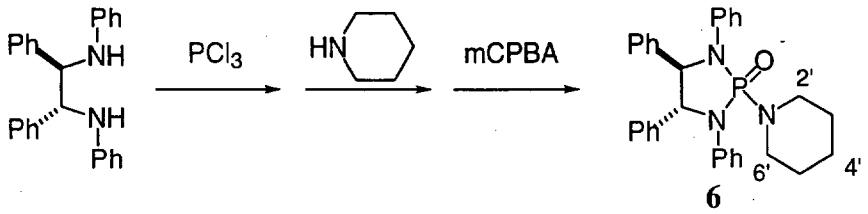
TLC: Rf 0.83 (EtOAc)

Anal.: $C_{27}H_{28}N_3OP$ (441.51)

Calcd.: C, 73.45; H, 6.39; N, 9.52; P, 7.02

Found: C, 73.32; H, 6.42; N, 9.61; P, 6.74

(*S,S*)-1,3,4,5-Tetraphenyl-2-piperidino-1,3,2-diazaphospholidine 2-Oxide (6)



6

To a stirred cold (-78 °C) solution of PCl_3 (69 μL, 0.79 mmol) in 3 mL of dry CH_2Cl_2 was added (*R,R*)-*N,N'*,1,2-tetraphenylethylenediamine[3] (261 mg, 0.716 mmol) in 3 mL of dry CH_2Cl_2 via a syringe under nitrogen. Then triethylamine (0.22 mL, 1.57 mmol) was added at the same temperature. The mixture was warmed to rt, stirred for 5 h, and then condensed under reduced pressure to remove the excess reagents (PCl_3 and triethylamine).

The residue was suspended in 4 mL of dry CH_2Cl_2 and stirred, to which was added piperidine (0.21 mL, 2.15 mmol) at rt under nitrogen. The mixture was stirred for 18 h and condensed under reduced pressure to remove excess piperidine.

The residue was dissolved in 5 mL of CH_2Cl_2. *m*-Chloroperoxybenzoic acid (50%, 250 mg; 0.72 mmol) in 5 mL of CH_2Cl_2 was added dropwise at 0°C. The mixture was allowed to warm to rt and stirred for 24 h. Then saturated aqueous $NaHCO_3$ was added with stirring. The aqueous layer was separated and extracted with CH_2Cl_2 twice. The combined organic solutions were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated to give a crude material, which was purified by chromatography on silica gel (CH_2Cl_2 then CH_2Cl_2/2-propanol, 100/1 as eluents) and recrystallized from hexane to give 196 mg (55 % yield) of (–)-**6** as a colorless amorphous solid.

(±)-1,3,4,5-Tetraphenyl-2-piperidino-1,3,2-diazaphospholidine 2-Oxide (6)

Following the above procedure, from (±)-*N,N'*,1,2-tetraphenylethylenediamine (1.09 g, 3.0 mmol) and PCl_3 (299 μL, 3.3 mmol), 0.62 (51 % yield) of (±)-**6** as a colorless amorphous solid after chromatography and recrystallization.

Analytical Data for (–)-**6**

M.W. 493.59

mp: 195-197 °C (hexane)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.25-7.20 (m, 8H), 7.19-7.13 (m, 6H), 7.103-7.06 (m, 2H), 7.00 (dd, J = 7.7, 0.9, 2H), 6.94 (t, J = 7.3, 1H), 6.91 (t, J = 6.4, 1H), 4.93 (d, J = 8.1, 1H, HC(4/5)), 4.88 (dd, J = 8.3, 6.8, 1H, H(5/4)), 3.40-3.32 (m, 2H, HC(1')), 3.18-3.08 (m, 2H, HC(1')), 1.46-1.38 (m, 4H, HC(2')H_2), 1.18-1.06 (m, 2H, HC(3'))

^{13}C NMR: (125 MHz, $CDCl_3$)

140.30 (d, J = 3.7, C(1")), 140.29 (d, J = 6.6, (C1")), 138.38 (d, J = 8.3,C(1'")), 138.30 (d, J = 4.6,(C1'")), 128.96, 128.60, 128.52, 128.05, 127.74, 127.54, 123.24, 122.20, 121.86, 121.83, 119.56, 119.53, 67.73 (d, J = 10.1, C(4/5)), 66.69 (d, J = 12.0, C(5/4)), 45.35 (d, J = 2.8, C(1')), 25.37 (d, J = 4.6, C(2')), 24.35 (C(3'))

^{31}P NMR: (162 MHz, $CDCl_3$)

17.30

IR: (KBr)

2989(W), 2940(m), 2899(w), 2854(w), 1599(m), 1493(s), 1456(m), 1385(m), 1377(m), 1361(w), 1353(w), 1341(w), 1308(w), 1294(m), 1279(w), 1262(m), 124(w), 1165(w), 1120(m), 1069(m), 1029 (w), 1001(w), 967(s), 917 (w), 836(w), 699(w)

MS: (EI, 70 eV)

494 (M^++1, 21), 493 (M^+, 50), 182 (43), 181 (100), 180 (39), 104 (10), 84 (25), 77 (18)

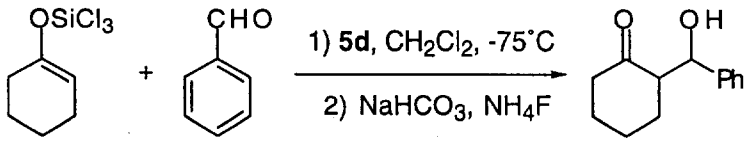
$[\alpha]_D^{25°C}$: -194° (c = 1.01, $CHCl_3$)

Analysis: ($C_{17}H_{24}O_2$)

Calcd:	C,	75.44%; H,	6.53%. N	8.51	P	6.28
Found:	C,	75.31%; H,	6.30%. N	8.46	P	6.09

TLC: R_f 0.89 (EtOAc)

General Procedure for Reactions between 1 and 2 Promoted by 5.



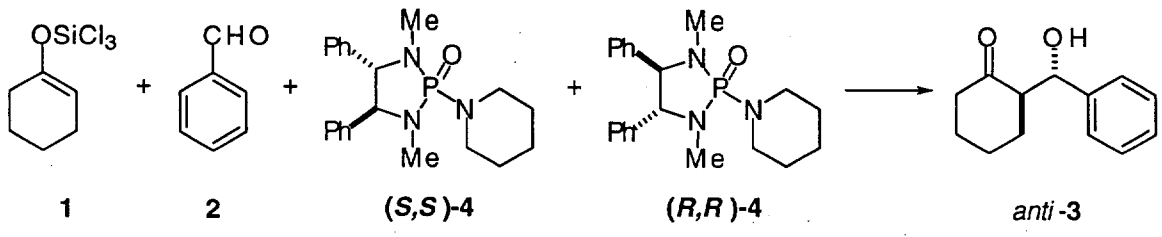
1 **2** *syn*-**3**

Phosphoramide **5d** (45.0 mg, 0.102 mmol) was dried at rt under high vacuum (ca. 0.05 mmHg) for 3 h in a two-necked round-bottomed flask. To this were added trichlorosilyl enolate **1** (0.20 mL, 1.1 mmol) and 10 mL of dry CH_2Cl_2 successively under nitrogen. After the solution was cooled to -75 °C (internal temperature, dry ice-2-propanol bath), benzaldehyde (0.10 mL, 0.98 mmol) was added dropwise and the mixture was stirred at -75 °C for 1.5 h.

The reaction mixture was poured into a mixture of 10 mL of saturated aqueous $NaHCO_3$ solution and 15 mL of 20% aqueous NH_4F solution at 0 °C and was stirred for 1 h at rt. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude products. The diastereomeric ratio was determined to be syn/anti, 40/1 by ^1H NMR. The crude mixture was purified by chromatography on silica gel (hexane/ethyl acetate, 10/1 then 5/1) to give 186.9 mg of *syn*-**3** and 3.7 mg of *anti*-**3**; total yield 95%.

General Procedures for Nonlinear Effect Studies

Procedure I (with phosphoramide **4**):

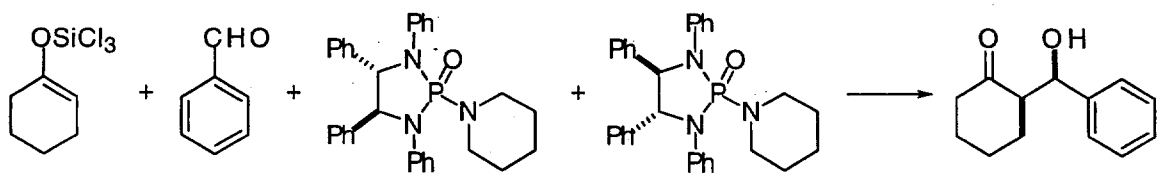


1 **2** **(*S,S*)-4** **(*R,R*)-4** ***anti*-3**

Phosphoramide (*S,S*)-**4** (25.89 mg, 0.0701 mmol) and (*R,R*)-**4** (11.11 mg, 0.0301 mmol) was weighed into a round bottomed flask and dried under high vacuum for 4 h. The phosphoramide (39.95% ee based on the weights) was then dissolved in dichloromethane (10 mL) under argon and the solution cooled to -78 °C. The trichlorosilyl enolate 1 (201 μL, 1.1 mmol) was then added via a syringe and solution stirred for 5 min. Benzaldehyde (102 μL, 1.0 mmol) was then added and the solution stirred at -78 °C fro 8 min. The reaction mixture was then poured into a mixture of saturated $NaHCO_3$ and 20% NH_4F solution at 0 °C with vigorous stirring. The mixture was then stirred at rt for 30 min. The layers were separated and the aqueous layer extracted with methylene chloride (2 × 20 mL). The combined organic solution was washed with brine, dried ($MgSO_4$) and concentrated to give oily residue, which was then purified by column chromatography (SiO_2, 9/1 to 3/1 hexane/EtOAc) to give 189 mg (93%) of *anti*-**3** along with 9.2 mg (5%)*syn*-**3**.

HPLC: t_R (1'*R*, 2*S*)-**3** = 13.68 min (23.35%), t_R (1'*S*, 2*R*)-**3**, 16.97 min (76.65%) (Daicel ChiralCel OJ, hexane/2-propanol, 90/10, 0.6 mL/min.).

Procedure II (with phosphoramide **6**):



1 **2** **(*S,S*)-6** **(±)-6** ***syn*-3**

A mixture of (*S,S*)-**6** (4.96 mg, 0.0101 mmol) and (±)-**6** (19.69 mg, 0.0399 mmol) was dried under high vacuum over night and then dissolved in methylene chloride (5 mL) under argon (20.1% ee of phosphoramide **6** based on weights). The solution was cooled to -78 °C and enolate **1** (100.3 μL, 0.55 mmol) was added. After the solution was stirred for 5 min at -78 °C benzaldehyde (50.8 μL, 0.50 mmol) was added and the solution was stirred at -78 °C for 2h. The reaction was then quenched by pouring into a mixture of saturated $NaHCO_3$ (6 mL) and 20% NH_4F (6 mL) solution at 0 °C with vigorous stirring. The mixture was then stirred at rt for 1h and then filtered through a layer of Celite. The layers of the filtrate were separated and the aqueous layer extracted with methylene chloride (2×10 mL). The combined organic solution was washed with brine, dried ($MgSO_4$) and concentrated to give solid residue, which was then purified by column chromatography (SiO_2, 9/1 hexane/EtOAc) to give *syn*-**3** (86.7 mg, 85%). HPLC analysis showed 11.3% ee for *syn*-**3**.

HPLC: t_R (1'*R*, 2*R*)-**3** = 13.32 min (55.65%); t_R (1'*S*, 2*S*)-**3**, 17.81 min (44.35%) (Daicel ChiralCel OJ, hexane/2-propanol, 90/10, 0.6 mL/min.).

General Procedure for Loading Effect of Phosphoramide on Syn/Anti Ratio.

Phosphoramide **5c** (18.5 mg, 0.054 mmol) was dried at rt under high vacuum (ca. 0.05 mmHg) for 3 h in a two-necked round-bottomed flask. Trichlorosilyl enolate **1** (0.10 mL, 0.55 mmol) and 5 mL of dry CH_2Cl_2 were added successively under nitrogen. After the solution was cooled to -75 °C (internal temperature, dry ice-2-propanol bath), benzaldehyde (0.20 mL, 1.97

mmol) was added dropwise and the mixture was stirred at -75 °C for 3 h. The quenching procedure and determination of the product ratio were the same as general phosphoramide-promoted reaction procedures.

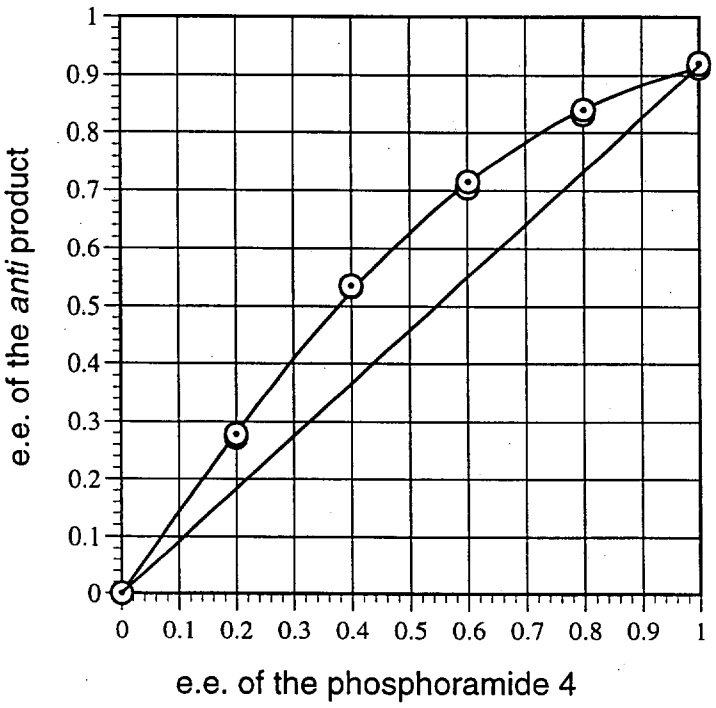
Curve Fitting in Nonlinear Effect Studies:

Assuming a statistical distributions of ligands, in a two ligand model the product ee can be expressed as a function of catalyst ee:[4]

$$ee_{prod} = ee_0 ee_{cat} \frac{2}{1+g+(1-g)ee_{cat}^2} \qquad (A)$$

A curve fitting with our data in this formula (ee expressed as decimal numbers), provides a good line fitting with g = 0.28 (where $g = k_{RS}/k_{RR}$, so the homochiral complex is 3.6 times as reactive as the meso complex) and $R^2 = 0.9997$:

Figure: Computed Curve Fitting with Two Ligand Model.



Also noted from the above equation (A) is that ee_{prod} is independent of catalyst concentration. A reservoir model resulting in nonlinear effects would show dependence of ee_{prod} on catalyst concentration. Considering a scenario at low enough concentrations of catalyst, one can see that a dimer which is in equilibrium with monomers in solution would mostly dissociate and therefore a linear dependence of ee_{prod} on ee_{cat} would be observed. By the same token, higher concentration of catalyst would show larger deviation from linearity. The fact that one of our control experiments with 1.0 equiv of phosphoramide gave essentially the same ee is inconsistent with reservoir model in nonlinear effects.

Kinetic Analysis for Loading Effect Studies:

To understand the origin of loading effect, we consider the following competitive reaction pathways:

$$\mathbf{A} + \mathbf{B} \xrightarrow{k_1} \mathbf{E} + \mathbf{E'} \quad (1)$$

$$\mathbf{A} + \mathbf{C} \xrightarrow{k_2} \mathbf{F} + \mathbf{F'} \quad (2)$$

$$\mathbf{B} + \mathbf{D} \overset{K}{\rightleftharpoons} \mathbf{C} \quad (3)$$

Reaction between **A** and **B** gives diastereomeric products **E** and **E'**; **A** reacts with **C** to give diastereomers **F** and **F'**; and **B** and **C** are related by the equilibrium in equation (3). We can write rate equations as following:

$$\frac{d([E]+[E'])}{dt} = k_1[A][B] \quad (4)$$

$$\frac{d([F]+[F'])}{dt} = k_2[A][C] \quad (5)$$

$$K = \frac{[C]}{[B][D]} \quad (6)$$

Dividing equation (4) by equation (5) and substituting for [**B**]/[**C**] from equation (6) we can derive:

$$\frac{d([E]+[E'])}{d([F]+[F'])} = \frac{k_1}{k_2 K}\frac{1}{[D]} \tag{7}$$

Assuming [**C**] is constant with time, we can integrate (7) to give equation (8):

$$[E]+[E'] = \frac{k_1}{k_2 K}\frac{1}{[D]}([F]+[F']) + constant \tag{8}$$

When $t = 0$, [**E**]+[**E'**]=0, [**F**]+[**F'**]=0, the constant in the above equation also equals zero. In the case that competitive pathways (1) and (2) give the same diastereomers with different ratio, i.e. **E**=**F**, **E'**=**F'**, we define:

$$\alpha = \frac{[E]}{[E']} \quad , \qquad \beta = \frac{[F]}{[F']} \tag{9}$$

and

$$K' = \frac{k_1}{k_2 K} \tag{10}$$

where α is the diastereomeric ratio of the product generated through pathway (1) and β is the diastereomeric ratio of the product generated through pathway (2). The observed diastereomeric ratio γ can be derived from (8):

$$\gamma = \frac{[E]+[F]}{[E']+[F']} = \frac{(1+\beta)\alpha K' + (1+\alpha)\beta[D]}{(1+\beta)K' + (1+\alpha)[D]} \tag{11}$$

If $\alpha \to \infty$, then equation 11 can be simplified as:

$$\gamma = \frac{[E]+[F]}{[E']+[F']} = (1+\beta)K'\frac{1}{[D]} + \beta \tag{12}$$

In the from our loading effect studies, let **A** be the aldehyde; **B** be the enolate-phosphoramide complex; **C** be the complex of enolate with two molecules of phosphoramide; **D** be the phosphoramide; **E** and **F** be the syn product and **E'** and **F'** be the anti product, then γ is the observed syn/anti ratio. According to equation (12), γ should be in reverse first order to the concentration of phosphoramide. This is exactly what we observed.

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