Supplementary Information

Subtleties in asymmetric catalyst structure: the resolution of a 6-phospha-2,4,8-trioxa-adamantane and its applications in asymmetric hydrogenation catalysis

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Resolution of CgPH according to Scheme 1.

(A) Preparation of CgP(O)OH

A MAJOR EXPLOSION OCCURRED RECENTLY DURING THE COURSE OF REPEATING THE SYNTHESIS OF THIS COMPOUND. PLEASE CONTACT THE AUTHOR (paul.pringle@bristol.ac.uk) FOR MORE DETAILS.

(B) Preparation of [CgP(O)O][QH] (Q = quinine)

To a boiling solution of CgP(O)OH (23.1 g, 93.0 mmol) in toluene (250 cm^3) in air was added quinine (30.0 g, 92.59 mmol). On cooling the reaction mixture, the product precipitated out as an off-white sponge-like solid. Upon removal of the solvent *in vacuo*, the precipitate became a fine white powder (48.04 g, 91.16 mmol, 98%). ^{31}P NMR (121 MHz; CD_2Cl_2): δ 20.38, 20.33. ^{1}H NMR (400 MHz; CD_2Cl_2): 8.68 (d, 1H, ^3J(HH) 4.64 Hz), 7.98 (d, 1H, J(HH) 9.04 Hz), 7.64 (d, 1H, ^3J(HH) 4.64 Hz), 7.41-7.15 (m, 5H), 5.94 (d, 1H, 2.44 Hz), 5.73-5.63 (m, 1H), 5.06-4.96 (m, 2H), 4.06-3.96 (m, 1H), 3.34-3.27 (m, 1H), 3.24 (dd, 1H, J(HH) 13.44 Hz, J(HH) 10.51 Hz), 2.95-2.88 (m, 1H), 2.87-2.78 (m, 1H), 2.46 (dd, 1H, J(HH) 12.71 Hz, J(HH) 1.71 Hz), 2.38 (s, 2H), 2.35 (dd, 1H, J(HH) 12.71 Hz, J(HH) 1.71 Hz), 2.01-1.91 (m, 3H), 1.80 (dd, 1H, ^3J(PH) 20.46 Hz, ^2J(HH) 12.95 Hz), 1.74 (dd, 1H, ^3J(PH) 20.46 Hz, ^2J(HH) 12.95 Hz), 1.68-1.58 (m, 1H), 1.47-1.38 (m, 1H), 1.33 (s, 3H), 1.22 (d, 3H, ^2J(PH) 11.24 Hz) 1.20 (d, 3H, ^2J(PH) 11.24 Hz). ^{13}C NMR (100 MHz; CD_2Cl_2): 158.09 (Ar*C*OCH_3), 147.60 (*C*H), 146.47, 144.26, 139.83 (*C*H), 138.05, 131.59 (*C*H), 129.08 (*C*H), 128.27 (*C*H), 126.37, 125.35 (*C*H), 121.19 (*C*H), 119.27 (*C*H), 115,54 (H_2C=C), 101.65 (*C*H), 96.25 (*pseudo*-t, 2.31 Hz), 72.69 (d, ^1J(PC) 93.78 Hz), 72.62 (d, ^1J(PC) 93.78 Hz), 68.38 (*C*H), 60.32 (*C*H), 56.12 (OCH_3), 55.30 (NCH_2), 44.47 (d, ^2J(PC) 3.08 Hz, CH_2), 44.37 (d, ^2J(PC) 3.08 Hz, CH_2), 43.54 (CH_2), 38.53 (*C*H), 27.58 (d, ^2J(PC) 2.31 Hz, CH_3), 27.49 (*C*H/CH_3), 25.88 (CH_2), 21.27 (*C*H/CH_3), 20.30 (CH_2), 19.58 (*C*H/CH_3), 19.56 (*C*H/CH_3).

(C) Separation of [β-CgP(O)O][QH]

[CgP(O)O][QH] (40.04 g, 91.16 mmol) was dissolved in a minimum (approx. 250 cm^3) of boiling toluene and the reaction mixture allowed to cool to room temperature. After 3 h, a thick white foam was formed which on filtration afforded a fine white powder. This process of

recrystallisation of the solid was repeated seven times until the ^{31}P NMR spectrum in CH_2Cl_2 showed only one signal. The recovery of the resolved [*β*-CgP(O)O][QH] (16.18 g, 81%). ^{31}P NMR (121 MHz; CD_2Cl_2): δ 20.38. ^{1}H NMR (300 MHz; CD_2Cl_2) 8.69 (d, 1H, ^{3}J(HH) 4.59 Hz), 7.98 (d, 1H, *J*(HH) 8.99 Hz), 7.76 (d, 1H, *J*(HH) 4.22 Hz), 7.66 (d, 1H, ^{3}J(HH) 4.59Hz), 7.33-7.08 (m, 4H), 6.23 (s, 1H), 5.60-5.49 (m, 1H), 5.02-4.92 (m, 2H), 4.43-4.30 (m, 1H), 3.95-3.88 (m, 3H), 3.39-3.27 (m, 2H), 3.11-3.03 (m, 1H), 2.93 (td, 1H, *J*(HH) 11.93 Hz, *J*(HH) 3.85 Hz), 2.58 (br s, 1H), 2.40 (dd, 2H, *J*(HH) 12.66 Hz, *J*(HH) 1.65 Hz), 2.32 (s, 1H), 2.11-1.95 (m, 3H), 1.77 (dd, 2H, ^{3}J(PH) 20.19 Hz, ^{2}J(HH) 12.85 Hz), 1.28 (s, 6H), 1.16 (d, 6H, ^{2}J(PH) 11.19 Hz). ^{13}C NMR (75 MHz; CD_2Cl_2): 158.18 (Ar*C*OCH_3), 147.72 (*C*H), 144.65, 144.23, 138.24 (*C*H), 131.59 (*C*H), 129.01 (*C*H), 128.20 (*C*H), 125.27, 120.86 (*C*H),119.42 (*C*H), 116.49 (H_2C=C), 101.26 (*C*H), 96.19, 72.64 (d, ^{1}J(PC) 93.46 Hz), 66.09 (*C*H), 60.15 (*C*H), 56.16 (O*C*H_3), 54.66 (N*C*H_2), 44.43 (d, *C*H_2), 44.00 (*C*H_2), 37.60 (*C*H), 27.54 (*C*H_3), 26.98 (*C*H/*C*H_3), 24.68 (*C*H_2), 21.19 (*C*H/*C*H_3), 19.51 (*C*H/*C*H_3), 18.78 (*C*H_2).

(D) Separation of [α-CgP(O)O][QH]

The toluene was removed *in vacuo* from the collected filtrates from the separation of the β-enantiomer (described above) to afford an off-white solid (21.47 g). This was then dissolved in a minimum of boiling toluene (50 cm^3). On cooling this solution, a white solid was formed which by ^{31}P NMR was > 90% α-enantiomer contaminated with *β*-enantiomer (5.13 g, 26%).

(E) Preparation of β-CgP(O)OH

To a solution of [*β*-CgP(O)O][QH] (0.572 g, 1.085 mmol) in CH_2Cl_2 (20 cm^3) was added aqueous NaOH (2M, 20 cm^3). The organic layer was separated and extracted with aqueous NaOH (2M, 3 x 5 cm^3). The aqueous layers were then combined and conc. 12M HCl (15 cm^3) was added. EtOH (50 cm^3) was then added to aid the evaporation of the water and the solvent removed *in vacuo*. The resulting precipitate was redissolved in boiling toluene (50 cm^3), hot filtered and the insoluble material washed with boiling toluene (3 x 10 cm^3). Removal of the toluene afforded crude CgP(O)OH (0.242 g, 0.977 mmol, 90%). The crude product was recrystallised from boiling ^{i}PrOH to yield colourless crystals (0.194 g, 0.781 mmol, 72%). $[\alpha]_D^{295}$ 42.2°.

(F) Preparation of β-CgPH

A two-necked flask was fitted with a condenser and charged with a solution of *β*-CgP(O)OH (0.790 g, 3.18 mmol) in Et_2O (30 cm^3) and cooled in an ice bath. $LiAlH_4$ (2M in THF, 6.4 cm^3, 12.80 mmol) was then added dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and left stirring overnight. A fresh ice bath was placed around the reaction mixture and the reaction mixture quenched by dropwise addition of deoxygenated aqueous HCl

(2M, 60 cm^3) over 2 h. CAUTION: quench is very exothermic and flammable gas is evolved rapidly. The reaction was deemed fully quenched after all aluminium salts were observed to have dissolved. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 20 cm^3). The Et_2O layers were combined, dried over $MgSO_4$ and then filtered. Removal of the solvent *in vacuo* afforded the white solid *β*-CgPH (0.118 g, 0.546 mmol, 17%).

Preparation of rac/meso-[$PdCl_2$(CgPH)$_2$] (1)

Racemic CgPH (0.019 g, 0.088 mmol) was dissolved in $CDCl_3$ (0.75 cm^3) and to this was added [$PdCl_2$(cod)] (0.013 g, 0.044 mmol) and the compound characterised *in situ* by ^{31}P NMR (121 MHz; $CDCl_3$): δ 3.5, 3.2. The pure [$PdCl_2$(*β*-CgPH)$_2$] was prepared in the same manner from β-CgPH. The non-decoupled ^{31}P NMR (121 MHz; $CDCl_3$): δ 3.5 (AA'XX', ^2J(PP') 514.6 Hz, ^1J(PH) 356.6 Hz, ^3J(PH') 6.3 Hz). ^{1}H NMR (300 MHz; $CDCl_3$): 4.88-3.66 (AA'XX' type m, 1H,) 2.78 (d, 1H, ^2J(PH) 13.40 Hz), 2.07-1.88 (m, 2H), 1.85-1.58 (m, 4H), 1.46-1.29 (m, 9H). ^{13}C NMR (75 MHz; $CDCl_3$): 96.88, 73.56, 72.54, 72.37, 46.73, 43.41, 39.85, 28.95, 27.90, 27.50.

Preparation of [Rh(cod)(β–CgPH)$_2$]BF_4 (2)

[$Rh(cod)_2$]BF_4 (47 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (5 mL) and *β*–CgPH (50 mg, 0.23 mmol) was added. The reaction mixture was stirred for 20 min and the solvent volume reduced to 2 mL. Addition of Et_2O (10 mL) resulted in a yellow precipitate, which was separated by filtration, washed with Et_2O (2 x 2 mL) and dried to give the product as an orange solid (30 mg, 60% yield). ^{31}P NMR (121 MHz; CD_2Cl_2): *δ* 15.5 (d, ^1J(RhP) = 141 Hz);

Preparation of β–CgPCH$_2$CH$_2$PH$_2$ according to Scheme 2

Diethyl vinylphosphonate (0.22 mL, 0.23 g, 1.4 mmol) was heated to 80 ˚C and solid *β*–CgPH (0.30 g, 1.4 mmol) was added to give a clear solution and then the radical initiator AIBN (15 mg) was added. The mixture was stirred and heated for 24 h. The flask was then evacuated at 80 ˚C to remove any volatiles. The intermediate *β*–CgPCH_2CH_2P(O)$(OEt)_2$ was characterised spectroscopically and used without further purification for the next step. ^{31}P NMR (121 MHz; $CDCl_3$): δ 31.0 (d, 65 Hz), -24.8 (d, 65 Hz). ^{1}H NMR (300 MHz; $CDCl_3$): 4.04 (m, 4H), 2.0-1.4 (m, 8H), 1.4-1.0 (m, 18H). The crude *β*–CgPCH_2CH_2P(O)$(OEt)_2$ was dissolved in Et_2O (5 mL) and added by syringe to a stirred, ice cold solution of $LiAlH_4$ (1.4 mL of 2M solution in THF, 2.8 mmol) in Et_2O (5 mL). The mixture was then allowed to warm to ambient temperature and after 40 min the ^{31}P NMR spectrum of the solution indicated complete reaction. Water (10 mL) was added dropwise over 5 min to quench the excess of $LiAlH_4$. The ether layer was separated and the aqueous layer extrated with Et_2O (2 x 5 mL). The combined extract was dried over $MgSO_4$,

filtered and solvent removed under reduced pressure to give the product as a colourless viscous oil (0.30 g, 78% yield). HRMS (ESI): 277.1128 $(MH)^+$ (calc. for $C_{12}H_{23}O_3P_2$ 277.1117). ^{31}P NMR (121 MHz; C_6D_6): -26.5 (d, ^3J(PP) 17 Hz, *P*Cg), -131.0 (dt, ^3J(PP) 17 Hz, ^1J(PH) 189 Hz, *P*H_2). ^{1}H NMR (300 MHz; C_6D_6): 2.74 (ddt, 1H, ^1J(PH) 191.03 Hz, ^2J(HH) 11.74 Hz, ^3J(HH) 7.16 Hz), 2.72 (ddt, 1H, ^1J(PH) 191.22 Hz, ^2J(HH) 11.74 Hz, ^3J(HH) 7.16 Hz), 1.82-1.58 (m, 3H), 1.50-1.38 (m, 2H), 1.37 (s, 3H), 1.34 (s, 3H), 1.26 (d, 2H, ^2J(PH) 13.20 Hz, CgPC*H*$_2$), 1.23 (d, 3H, ^3J(PH) 12.85 Hz), 1.15 (d, 3H, ^3J(PH) 12.11 Hz), 1.00-0.85 (m, 1H). ^{13}C NMR (75 MHz; C_6D_6) 96.58, 95.68, 72.13, 71.93 (d, ^1J(PC) 13.85 Hz), 37.11 (*C*H_2), 28.08 (*C*H_3), 27.92 (*C*H_3), 27.78 (*C*H_3), 26.80 (d, ^2J(PC) 12.69 Hz, *C*H_3), 24.68 (d, ^1J(PC) 25.38 Hz, *C*H_2), 12.98 (dd, ^1J(PC) 24.81 Hz, ^2J(PC) 9.81 Hz, *C*H_2).

Preparation of β–CgPCH$_2$CH$_2$P(R,R-CHMeCH$_2$CH$_2$CHMe) (L$_a$)

β–CgPCH$_2$CH$_2$PH$_2$ (95 mg, 0.34 mmol) and (*2S,5S)*-2,5-hexanediol cyclic sulphate (62 mg, 0.34 mmol) were dissolved in THF (10 mL) and stirred. ^{n}BuLi (0.65 mL, 1.6M solution in hexanes, 1.0 mmol) added dropwise over 5 min. After 45 min the ^{31}P NMR spectrum of the reaction mixture showed complete conversion. Water (5 mL) was added, the ether layer was separated and the aqueous layer extrated with Et_2O (2 x 5 mL). The combined extract was dried over $MgSO_4$, filtered and solvent removed under reduced pressure to give **L$_a$** as a colourless viscous oil (0.11 g, 94% yield). ^{31}P NMR (121 MHz; CD_2Cl_2): *δ* 4.6 (d, ^3J(PP) 30 Hz, phospholane), -24.4 (d, ^3J(PP) 30 Hz, *P*Cg).

Preparation of β–CgPCH$_2$CH$_2$P(S,S-CHMeCH$_2$CH$_2$CHMe) (L$_b$)

Ligand **L**$_b$ was made in the same way as described for **L$_a$** above using (*2R,5R)*-2,5-hexanediol cyclic sulphate. HRMS (EI): 358.1837 $(M)^+$ (calc. for $C_{18}H_{32}O_3P_2$ 358.1827). ^{31}P NMR (121 MHz; CD_2Cl_2): *δ* 4.9 (d, ^3J(PP) 28 Hz, phospholane), -23.8 (d, ^3J(PP) 28 Hz, *P*Cg).

Preparation of [RhL$_a$(cod)]BF$_4$ (3a)

A solution of **L$_a$** (50 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) was added to a solution of [Rh(cod)$_2$]BF_4 (57 mg, 0.14 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 20 min and the solvent volume reduced to 2 mL. Addition of Et_2O (10 mL) resulted in a yellow precipitate, which was separated by filtration, washed with Et_2O (2 x 2 mL) and dried to give the product as an orange solid (40 mg, 44% yield). HRMS (ESI): 569.1812 $(M)^+$ (calc. for $C_{26}H_{44}O_3P_2Rh$ 569.1815). ^{31}P NMR (121 MHz; CD_2Cl_2): 82.7 (dd, ^1J(RhP) 141 Hz, ^2J(PP) 19 Hz, phospholane), 45.2 (dd, ^1J(RhP) = 154 Hz, ^2J(PP) = 19 Hz, *P*Cg). ^{1}H NMR (300 MHz; CD_2Cl_2): 6.3 (1H, s broad, COD), 5.4 (1H, s broad, COD), 5.3 (1H, s broad, COD), 4.9 (1H, s broad, COD), 2.7-1.1 (40H, m). ^{13}C NMR (75 MHz; CD_2Cl_2): 104.0 (dd, *J*(RhC) 7.2 Hz, *J*(PC) 6.2 Hz, COD), 102.9 (dd,

J(RhC) 9.5 Hz, *J*(PC) 6.1 Hz, COD), 100.3 (t, *J*(RhC) = *J*(PC) 7.8 Hz, COD), 97.2 (d, *J*(PC) 1.2 Hz, *C*O_2CH_3), 97.0 (d, *J*(PC) 1.0 Hz, *C*O_2CH_3), 93.3 (dd, *J*(RhC) 9.4 Hz, *J*(PC) 7.5 Hz, COD), 74.6 (dd, *J*(PC) 22.6 Hz, *J*(RhC) 1.2 Hz, *C*OCH_3), 74.6 (dd, *J*(PC) 12.5 Hz, *J*(RhC) 2.0 Hz, *C*OCH_3), 42.9 (d, *J*(PC) 6.9 Hz), 40.1, 38.5 (d, *J*(PC) 1.4 Hz), 38.2 (d, *J*(PC) 1.7 Hz), 36.7 (d, *J*(PC) 1.0 Hz), 34.8 (d, *J*(PC) 1.3 Hz), 33.8 (m), 33.5 (m), 32.4 (m), 28.7 (t, *J*(PC) 1.7 Hz), 28.5, 28.3 (d, *J*(PC) 10.1 Hz), 27.6 (d, *J*(PC) 12.8 Hz), 27.6 (d, *J*(PC) 7.3 Hz), 20.7 (74.6 (dd, *J*(PC) 6.6 Hz, *J*(RhC) 0.9 Hz).

Preparation of [RhL$_b$(cod)]BF$_4$ (3b)

Complex **3b** was made in the same way as described for **3a** above using $\mathbf{L_b}$. HRMS (ESI): 569.1795 $(M)^+$ (calc. for $C_{26}H_{44}O_3P_2Rh$ 569.1815). ^{31}P NMR (202 MHz; CD_2Cl_2): δ 80.0 (dd, ^{1}*J*(RhP) 140 Hz, ^{2}*J*(PP) 19 Hz, phospholane), 44.9 (dd, ^{1}*J*(RhP) 154 Hz, ^{2}*J*(PP) 19 Hz, *P*Cg). ^{1}H NMR (500 MHz; CD_2Cl_2): 6.1 (1H, s broad, COD), 5.6 (1H, s broad, COD), 5.2 (1H, s broad, COD), 4.8 (1H, s broad, COD), 2.7-1.1 (40H, m). ^{13}C NMR (126 MHz; CD_2Cl_2): 104.0 (dd, *J*(RhC) 7.8 Hz, *J*(PC) 6.4 Hz, COD), 100.4 (t, *J*(RhC) = *J*(PC) 8.3 Hz, COD), 99.5 (dd, *J*(RhC) 8.3 Hz, *J*(PC) 5.9 Hz, COD), 97.3 (s, broad, *C*O_2CH_3), 97.0 (s, broad, *C*O_2CH_3), 92.0 (dd, *J*(RhC) 10.3 Hz, *J*(PC) 6.9 Hz, COD), 75.7 (d, *J*(PC) 22.6 Hz, *C*OCH_3), 74.5 (dd, *J*(PC) 13.2 Hz, *J*(RhC) 2.0 Hz, *C*OCH_3), 42.4 (d, *J*(PC) 6.4 Hz), 40.7 (d, *J*(PC) 25.9 Hz), 39.8, 37.3 (d, *J*(PC) 2.0 Hz), 35.6 (d, *J*(PC) 1.5 Hz), 32.9 (dd, *J*(PC) 24.5 Hz, *J*(RhC) 1.0 Hz,), 31.5 (d, broad, *J*(PC) 7.3 Hz), 30.7 (t, *J*(PC) 1.8 Hz), 30.4 (t, *J*(PC) 2.7 Hz), 30.3, 29.9 (dd, *J*(PC) 10.8 Hz, *J*(RhC) 1.0 Hz), 27.6 (d, *J*(PC) 22.0 Hz), 26.7 (d, *J*(PC) 6.9 Hz), 20.3 (d, *J*(PC) 7.3 Hz).

Hydrogenation Catalysis

The substrate (MAA or MAC) (50 mg) and catalyst (1 mol %) were placed in a stainless steel autoclave, put under N_2 atmosphere and solvent (5 cm^3) was added *via* syringe. The autoclave was then purged and pressurised with 5 bar H_2. After 1 h stirring the mixture at ambient temperature, the autoclave was depressurised and samples for GC analysis were prepared by dissolving 0.1 mL of the reaction mixture with 1.6 mL of CH_2Cl_2 in a GC vial.

GC conditions for MAA and MAC enantiomers resolution

MAA: Varian CP-Chirasil-DEX CB (25m) column
90˚C for 1 min then 5˚C/min to 140˚C for 10 min
8.37 min (*S*), 8.64 min (*R*)

MAC: Varian CP-Chirasil-DEX CB (25m) column
120˚C for 1 min then 3˚C/min to 175˚C for 18 min then 175˚C for 11 min
19.61 min (*R*), 19.76 min (*S*)

Crystal structure determination

Details of crystal data are presented in Table S1. X-ray diffraction experiments carried out at 100 K on a Bruker Kappa Apex II CCD diffractometer using Mo-K_α radiation (λ = 0.71073 Å). Intensities were integrated[i] from several series of exposures in φ and ω calculated by the Apex II[ii] program after unit cell determination. Absorption corrections were based on equivalent reflections using SADABS,[iii] and structures were refined against all F_o^2 data with hydrogen atoms (on carbon atoms) riding in calculated positions using SHELXTL.[iv] For *β*-CgPH, one of the two independent molecules in the unit cell has the hydrogen atom bonded to the phosphorus atom is disordered over two sites. The P-H bond lengths were restrained to mimic that in the other molecule in the crystal structure.

Table S1 Crystal data

Compound	*β*-CgPOOH	*β*-CgPH	[Rh(COD)(*β*-CgP-C_2H_4-PC_6H_{10})]BF_4
Colour, habit	colourless cut-block	colourless block	orange lump
Size/mm	0.341x0.314x0.132	0.151x0.096x0.065	0.156x0.079x0.072
Empirical Formula	$C_{10}H_{17}O_5P$	$C_{10}H_{17}O_3P$	$C_{26}H_{44}BF_4O_3P_2Rh$
M	248.21	216.21	656.27
Crystal system	orthorhombic	monoclinic	orthorhombic
Space group (No.)	*P* $2_12_12_1$ (19)	*P* 2_1 (4)	*P* $2_12_12_1$ (19)
a/Å	7.4965(4)	8.1704(9)	9.7901(13)
b/Å	7.9821(3)	8.0964(8)	12.3119(17)
c/Å	19.2574(10)	17.027(2)	23.759(3)
α/°	90.00	90.00	90.00
β/°	90.00	96.726(2)	90.00
γ/°	90.00	90.00	90.00
V/A^3	1152.32(10)	1118.6(2)	2863.8(7)
Z	4	4	4
μ/mm^{-1}	0.242	0.226	0.761
T/K	100	100	100
Reflections: total/independent	7138/2646	12572/4484	22387/6590
R_{int}	0.0309	0.0707	0.0718
Final *R*1 (observed data)	0.0315	0.0508	0.0455
Largest peak, hole (eA^{-3})	0.611, -0.307	0.344, -0.293	1.349, -0.807
ρ_{calc}/g cm^{-3}	1.431	1.284	1.522

References

[i] SAINT v7.34A, Bruker-AXS, 2007.
[ii] Apex2, Bruker-AXS, 2007.
[iii] G. M. Sheldrick (2008), SADABS V2008/1, Bruker AXS Inc., Madison, Wisconsin, USA.
[iv] SHELXTL program system version V 6.14, Bruker AXS Inc., Madison, Wisconsin, USA, 2000-3.