Supporting Information

Diastereo- and Enantioselective Synthesis of Nitroso Diels-Alder-type Bicycloketones Using Dienamine: Mechanistic Insight into Sequential Nitroso Aldol / Michael Reaction and Application for Optically Pure 1-Amino-3,4-diol Synthesis

Norie Momiyama, Yuhei Yamamoto and Hisashi Yamamoto*

*Department of Chemistry, University of Chicago,
5735 S. Ellis Avenue. Chicago, Illinois, 60637*

Experimental Section.

General. All reactions were carried out under an atmosphere of standard grade argon or nitrogen gas (oxygen <10 ppm) in flame-dried glassware with magnetic stirring. *n*-Hexane, CH₂Cl₂ and toluene were used as dried through almina in solvent line purification system. Anhydrous *n*-Pentane was purchased from Aldrich. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl under an atmosphere of dry argon. Nitrosobenzene was purchased from Tokyo Chemical Industry or Aldrich. 2-Cyclohepten-1-one was distilled under P₂O₅. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (E. Merck 230-400 mesh), silica gel 60 silanized (E. Merck) and Florisil® (Wako Pure Chemical or ACROS 60-100 mesh). Analytical thin layer chromatography (TLC) was performed on E. Merck precoated (0.25 mm) silica gel 60-F₂₅₄ plates. Visualization was accomplished with UV light and phosphomolybdic acid solution in ethanol by heating.

Infrared (IR) spectra were recorded on a Nicolet 20 SXB FTIR. ¹H NMR spectra were recorded on a Bruker DRX-500 (500 MHz), 400 (400 MHz) at ambient temperature. All NMR solvents were purchased from ACROS or Aldrich and used as received. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, coupling constant (Hz) and assignment. ¹³C NMR was recorded on a Bruker DRX-500 (125 MHz), 400 (100 MHz) at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, with solvent resonance employed as internal standard (deuteriochloroform at 77.0 ppm). High-performance liquid chromatography (HPLC) was performed on a Shimadzu 10A or Varian ProStar Series equipped with a variable wavelength detector using a Chiralpak AD, AD-H or Chiralcel OD-H column (0.46 cm x 25 cm) from Daicel. Optical rotations were measured on a JASCO DIP-1000 polarimeter and reported as follows: $[\alpha]_{\lambda}^{T^{\circ}\text{C}}$ (c=g/100 ml, solvent). Mass spectra were obtained on QSTAR (Applied SCIEX Biochemistry/MDS) spectrometers and JMS700 (JEOL) spectrometers in Chemical Instrument Center of Nagoya University and Graduate school of Engineering, Nagoya University or Kratos MS-30 in department of Chemistry, the University of Chicago. Elemental analysis was measured in Graduate school of Agriculture, Nagoya University. X-ray crystallographic data was collected using SMART APEX CCD (BRUKER AXS) based diffraction meter equipped with a low-temperature apparatus.

Preparation of dienamine. The synthesis of dienamines was prepared according to the reported procedure¹ and the chemical data were described in literature: A solution of the α,β -unsaturated ketone (1 equiv, 40 mmol) and amine (2 equiv, 80 mmol) in toluene (30 mL) was refluxed under the argon atmosphere for 15 ~ 35 h until all the water was separated on Dean-Stark trap. After evaporation of the solvent, the residue was distilled at reduced pressure.

General procedure for the preparation of binaphthol derivatives.

The synthesis of (*S*)-(-)-3,3'-Bis(triarylsilyl)-1,1'-bi-2-naphthols were prepared according to the reported procedure² and the chemical data were described in literature: To a solution of (*S*)-(-)-3,3'-dibromo-1,1'-bi-2-naphthol³ (1 equiv, 1.1 g, 2.5 mmol) was dissolved in DMF (25 mL), and imidazole (3 equiv, 510.6 mg, 7.5 mmol) followed by triarylsilyl halide (2.5 equiv) was added at room temperature. After stirring at 60 °C for 5 h, resulting solution was poured into saturated NaHCO₃, and extracted with CH₂Cl₂. The organic layers were washed again saturated NaHCO₃, dried over Na₂SO₄, and concentrated. The crude solid was purified by silica gel column chromatography (CH₂Cl₂/hexane = 1:2 as eluant) to furnish bis (triarylsilyl ether). To a solution of bromo silyl ether (1 equiv) in dry THF (30 mL) was added dropwise a 1.5 M *t*-BuLi in pentane (4 equiv) over 10min at 0 °C. The mixture was stirred at room temperature for 30 min, poured into saturated NH₄Cl and extracted with CH₂Cl₂. The combined extracts were dried over Na₂SO₄, and concentrated. The crude product was purified by column chromatography on silica gel (benzene/hexane = 1:2 as eluant) to give desired binaphthol derivatives.

(*S*)-(-)-3,3'-Bis(tri *m*-xylylsilyl)-1,1'-bi-2-naphthol. TLC R_f 0.62 (CH₂Cl₂/Hexane, 1:1); $[\alpha]_D^{27}$ -132 (c = 1.00, THF); ¹H NMR (CDCl₃, 400 MHz) δ 7.88 (s, 2H, Ar-*H*), 7.72 (d, 2H, J = 8.0 Hz, Ar-*H*), 7.24-7.33 (m, 18H, Ar-*H*), 7.02 (s, 6H, Ar-*H*), 5.25 (s, 2H, OH), 2.23 (s, 36H, CH₃). MS (CI) Exact Mass Calcd for C₁₄H₁₇NO₂ (M+H)⁺: 970.3. Found: 970.3.

General procedure for the preparation of tri *m*-xylylsilane.

To a solution of 5-Iodo-*m*-xylene (3 equiv, 4.3 mL, 30 mmol) in Et₂O (150 mL) was added 1.6 M *n*-BuLi in hexane (6 equiv, 37.5 mL, 60 mmol) at 0 °C and stirred at this temperature for 4 h. To a resulting solution was added trichlorosilane (1 equiv, 1.0 mL, 10 mmol) at 0 °C. After string at room temperature for 12 h, the reaction was quenched by MeOH, wash with saturated NaHCO₃ three times and extracted with Et₂O. The combined extracts were dried over Na₂SO₄, and concentrated. The crude product was purified by column chromatography on silica gel (hexane/CHCl₃ = 15:1 as eluent) to give desired tri *m*-xylylsilane in 64 %yield.

tri *m*-xylylsilane. Purification by flash column chromatography with elution by (1:30 CHCl₃: Hexane) provided as a whitish powder (64 % yield). TLC *R_f* 0.37 (CHCl₃/Hexane, 1:10); ¹H NMR (CDCl₃, 400 MHz) δ7.19 (s, 6H, Ar-*H*), 7.05 (s, 3H, Ar-*H*), 5.32 (s, 1H, SiH), 2.29 (s, 18H, CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ137.3 (6C), 133.4 (3C), 131.5 (3C), 21.3 (6C).

General procedure for the preparation of triarylsilane

To a solution of triarylsilane (1 equiv, 1.25 mmol) in CCl₄ (5 mL) was added bromine (1.2 equiv, 1.5 mmol) dropwise over 5 min at 0 °C and stirred at this temperature. After the triarylsilane was consumed (10 ~ 30 min), the resulting solution was evaporated to remove solvent and concentrated. The obtained crude product was used without purification for next step.

tri *m*-xylylsilylbromide. This was used without purification for next step. TLC *R_f* 0.45 (EtOAc/Hexane, 1:5); ¹H NMR (CDCl₃, 400 MHz) δ7.24 (s, 6H, Ar-*H*), 7.05 (s, 3H, Ar-*H*), 2.30 (s, 18H, CH₃).

General procedure for the reaction of 1,3-cyclohexa-dienamine with nitrosobenzene catalyzed by chiral binaphthol (N-Nitroso aldol / Michael Reaction).

A dried schlenk tube was charged with nitrosobenzene (1 equiv, 53.6 mg, 0.5 mmol) and chiral binaphthol derivative (30 mol%). CH₂Cl₂ (0.5 mL) was added by syringe and the resulting mixture was stirred at room temperature. After 30 min, anhydrous pentane (4.5 mL) was further added to the mixture of nitrosobenzene and catalyst solution. After cooling to -88 ~ -78 °C, dienamine (1.5 equiv, 0.75 mmol) in corresponding mixed solvent (0.5 ml) was added dropwise for 1 h. The mixture was stirred at -88 ~ -78 °C for 12 ~ 48 h. The reaction mixture was quenched by 1N HCl / THF (1:1) (0.5 mL) at -78 °C and the aqueous layer was treated with 1N NaOH (1 mL). The resulting solution was extracted with Et₂O and the combined organic extracts were washed with brine, dried over Na₂SO₄ with cooling and concentrated under reduced pressure after filtration. The

residual crude product was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane as the eluant to give the product.

7,7-Dimethyl-3-phenyl-2-oxa-3-aza-bicyclo[2.2.2]octan-5-one. Purification by flash column chromatography with elution by hexane:ethyl acetate:triethyl amine (30:1:0.1) provided as colorless oil. TLC R_f = 0.25 (5:1 hexane: ethyl acetate); $[\alpha]_D^{27}$ -300 (c = 1.50, CHCl_3); IR (CHCl_3) 2964, 2874, 1737, 1596, 1490, 849, 773, 694; ^1H NMR (CDCl_3 , 400 MHz) δ 7.26 (t, 2H, J = 8.3 Hz, Ar- H), 7.03 (d, 2H, J = 8.0 Hz, Ar- H), 6.92 (t, 1H, J = 7.5 Hz, Ar- H), 4.10 (m, 2H, CH), 2.63 (dd, J = 19.0, J = 2.4 Hz, 1 H), 2.49 (dd, J = 19.0 Hz, J = 3.3 Hz, 1 H), 2.29 (dd, J = 14.1 Hz, J = 3.3 Hz, 1 H), 1.96 (dd, J = 14.0 Hz, J = 3.5 Hz, 1 H), 1.35 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.4, 151.1, 129.0 (2C), 121.9, 114.8 (2C), 81.3, 64.8, 40.3, 38.4, 32.7, 28.4, 26.3; MS (CI) Exact Mass Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$ ($\text{M}+\text{H}^+$): 232.1. Found: 232.1. Enantiomeric excess was determined by HPLC with Chiralcel AD-H column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 13.2 min, minor enantiomer t_r = 7.4 min.

3-(4-Bromophenyl)-7,7-dimethyl-2-oxa-3-azabicyclo[2.2.2]octan-5-one. Purification by flash column chromatography with elution by hexane:ethyl acetate:triethyl amine (30:1:0.1) provided as white solid. TLC R_f = 0.21 (5:1 hexane: ethyl acetate); $[\alpha]_D^{29}$ -206 (c = 0.20, CHCl_3); IR (CHCl_3) 2967, 1735, 1507, 1490, 1399, 1216, 825, 770, 669; ^1H NMR (CDCl_3 , 400 MHz) δ 7.36 (d, 2H, J = 9.2 Hz, Ar- H), 6.90 (d, 2H, J = 8.0 Hz, Ar- H), 4.11 (t, 1H, J = 2.8 Hz), 4.05 (t, 1H, J = 3.2 Hz), 2.65 (dd, J = 19.0, J = 2.4 Hz, 1 H), 2.45 (dd, J = 19.0 Hz, J = 3.3 Hz, 1 H), 2.28 (dd, J = 14.1 Hz, J = 3.3 Hz, 1 H), 1.97 (dd, J = 14.1 Hz, J = 3.4 Hz, 1 H), 1.34 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 205.7, 150.2, 131.9 (2C), 116.5 (2C), 114.4, 81.4, 64.7, 40.3, 38.3, 32.6, 28.3, 26.3; MS (CI) Exact Mass Calcd for $\text{C}_{14}\text{H}_{16}\text{BrNO}_2$ ($\text{M}+\text{H}^+$): 310.0. Found: 310.0; Enantiomeric excess was determined by HPLC with Chiralcel AD-H column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 22.1 min, minor enantiomer t_r = 12.2 min.

3-(Biphenyl-4-yl)-7,7-dimethyl-2-oxa-3-azabicyclo[2.2.2]octan-5-one. Purification by flash column chromatography with elution by hexane:ethyl acetate (20:1) provided as yellowish solid. TLC R_f = 0.18 (5:1 hexane: ethyl acetate); $[\alpha]_D^{26}$ -275 (c = 0.29, CHCl_3); IR (CHCl_3) 2976, 1735, 1517, 1485, 1399, 1216, 1031, 837, 757; ^1H NMR (CDCl_3 , 400 MHz) δ 7.54 (d, 2H, J = 6.7 Hz, Ar- H), 7.50 (d, 2H, J = 5.4 Hz, Ar- H), 7.40 (t, 2H, J = 6.3 Hz, Ar- H), 7.31 (t, 1H, J = 6.0 Hz, Ar- H), 7.09 (d, 2H, J = 5.4 Hz, Ar- H), 4.13-4.15 (m, 2H), 2.66 (dd, J = 15.2, J = 1.9 Hz, 1 H), 2.54 (dd, J = 15.2 Hz, J = 2.6 Hz, 1 H), 2.32 (dd, J = 11.4 Hz, J = 2.7 Hz, 1 H), 1.98 (dd, J = 11.3 Hz, J = 2.8 Hz, 1 H), 1.34 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (100 MHz, CD_3Cl) δ 206.4, 150.5, 140.5, 134.7, 128.6 (2C), 127.6 (2C), 126.7, 126.6 (2C), 115.1 (2C), 81.5, 64.8, 40.4, 38.4, 32.7, 28.4, 26.4; MS (CI) Exact Mass Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_2$ ($\text{M}+\text{H}^+$): 308.1. Found: 308.1; Enantiomeric excess was determined by HPLC with

Chiralcel AD-H column (95.2:4.8 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 32.5 min, minor enantiomer t_r = 15.8 min.

7,7-dimethyl-3-(4-phenoxyphenyl)-2-oxa-3-aza-bicyclo[2.2.2]

octan-5-one. Purification by flash column chromatography with elution by hexane:ethyl acetate (20:1) provided as yellowish solid. TLC R_f = 0.18 (5:1 hexane: ethyl acetate); $[\alpha]_D^{26}$ -250 (c = 0.29, CHCl_3); IR (CHCl_3) 3019, 2400, 2361, 2337, 1734, 1216, 929, 756; ^1H NMR (CDCl_3 , 400 MHz) δ 7.30 (t, 2H, J = 7.6 Hz,

Ar- H), 7.00-7.08 (m, 3H, Ar- H), 6.92-6.96 (m, 4H, Ar- H), 4.12 (t, 1H, J = 2.6 Hz), 4.05 (t, 1H, J = 3.3 Hz), 2.67 (dd, J = 19.0, J = 2.2 Hz, 1 H), 2.54 (dd, J = 19.0 Hz, J = 3.3 Hz, 1 H), 2.30 (dd, J = 14.1 Hz, J = 3.3 Hz, 1 H), 1.96 (dd, J = 14.1 Hz, J = 3.4 Hz, 1 H), 1.56 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.6, 157.8, 151.6, 147.0, 129.6 (2C), 122.8, 120.0 (2C), 118.1 (2C), 116.4 (2C), , 81.4, 65.2, 40.4, 38.3, 32.6, 28.4, 26.5; MS (CI) Exact Mass Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 324.1, Found: 324.1; Enantiomeric excess was determined by HPLC with Chiralcel AD-H column (97.5:2.5 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 38.3 min, minor enantiomer t_r = 21.9 min.

3-(3,5-dimethylphenyl)-7,7-dimethyl-2-oxa-3-aza-bicyclo[2.2.2]

octan-5-one. Purification by flash column chromatography with elution by hexane:ethyl acetate:triethyl amine (30:1:0.1) provided as colorless oil. TLC R_f = 0.29 (5:1 hexane: ethyl acetate); $[\alpha]_D^{29}$ -288 (c = 0.30, CHCl_3); IR (CHCl_3) 2963, 2873, 1738, 1596, 1216, 1181, 1031, 993, 924, 835, 756; ^1H NMR (CDCl_3 , 400 MHz)

δ 6.65 (s, 2H, Ar- H), 6.58 (s, 2H, Ar- H), 4.10 (t, 1H, J = 2.2 Hz), 4.08 (t, 1H, J = 2.7 Hz), 2.63 (dd, J = 15.1, J = 1.9 Hz, 1 H), 2.53 (dd, J = 15.1 Hz, J = 2.6 Hz, 1 H), 2.28 (dd, J = 11.2 Hz, J = 2.6 Hz, 1 H), 2.26 (s, 6H, CH_3), 1.95 (dd, J = 11.2 Hz, J = 2.8 Hz, 1 H), 1.35 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.7, 151.2, 138.6, 123.8, 112.7 (2C), 81.4, 64.9, 40.4, 38.6, 32.8, 28.4, 26.4, 21.6; MS (CI) Exact Mass Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$: 260.1, Found: 260.1; Enantiomeric excess was determined by HPLC with Chiralcel AD-H column (95.2:4.8 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 17.3 min, minor enantiomer t_r = 6.8 min.

3,7,7-triphenyl-2-oxa-3-aza-bicyclo[2.2.2]octan-5-one.

Purification by flash column chromatography with elution by hexane:toluene (1:3) provided as yellowish solid. TLC R_f = 0.16 (1:5 hexane:benzene); IR (CHCl_3) 3019, 2400, 1739, 1391, 1216, 1149, 1008, 929, 771; ^1H NMR

(CDCl_3 , 400 MHz) δ 7.38 (d, 2H, J = 6.0 Hz, Ar- H), 7.33 (t, 2H, J = 5.9 Hz, Ar- H), 7.15-7.88 (m, 6H, Ar- H), 7.08 (dd, 4H, J = 18, 6.2 Hz, Ar- H), 5.41 (t, 1H, J = 2.1 Hz), 4.33 (t, 1H, J = 2.3 Hz), 3.52 (dd, J = 12.0, J = 3.2 Hz, 1 H), 2.92 (dd, J = 12.0 Hz, J = 2.2 Hz, 1 H), 2.41 (dd, J = 16.0 Hz, J = 2.8 Hz, 1 H), 2.00 (dd, J = 15.2 Hz, J = 1.8 Hz, 1 H), 1.99 (d, J = 1.8 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 205.0, 150.6, 148.9, 143.5, 129.3 (2C), 128.8 (2C), 128.4 (2C), 128.2, 127.2, 127.1 (2C), 126.9, 126.2, 122.2, 114.9 (2C), 78.1, 64.8, 48.6, 40.5, 35.6; MS (CI) Exact Mass Calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$: 355.2,

Found: 355.2; Enantiomeric excess was determined by HPLC with Chiralcel AD-H column (9:1 hexane:2-propanol), 1.0 mL/min; t_r = 11.8 min, 15.9 min.

6-(hydroxy(phenyl)amino)-4,4-diphenylcyclohex-2-en-1-one.

Purification by flash column chromatography with elution by (1:10 EtOAc: Hexane) provided as a yellowish powder. TLC R_f 0.25 (EtOAc/Hexane, 1:3); $[\alpha]_D^{29}$ -28.8 (c = 0.25, CHCl_3); IR (CHCl_3) 3019, 2400, 1685, 1598, 1492, 1216, 1103, 1031, 929, 757, 669; ^1H NMR (CDCl_3 , 400 MHz) δ 7.08-7.34 (m, 13H, Ar- H), 6.91 (t, 3H, J = 7.1 Hz, Ar- H), 6.78 (d, 2H, J = 7.7 Hz, Ar- H), 6.30 (d, 1H, J = 10.1 Hz, Ar- H), 5.82 (s, 1H, NOH), 4.38 (dd, 1H, J = 13.1, 3.4 Hz, CH), 3.06 (t, 1H, J = 12.9, CH_2), 2.65 (dt, 1H, J = 12.9, 2.8 Hz, CH_2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 196.5, 156.3, 149.5, 146.8, 142.6, 128.7, 128.6, 127.7, 126.6, 127.3, 127.1, 126.9, 121.4, 115.3, 66.7, 50.9, 34.6, 22.6; MS (CI) Exact Mass Calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_2$ (M) $^+$: 356.4. Found: 356.4. Enantiomeric excess was determined by HPLC with Chiralcel AD-H column (9:1 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 21.8 min, minor enantiomer t_r = 20.0 min.

General procedure for the preparation of authentic cycloadduct.

The authentic compound was prepared by the reaction of aromatic nitroso compounds (1 equiv, 0.3 mmol) and corresponding dienamine (1.5 equiv, 0.3 mmol) with (racemic)-BINOL (10 mol%) in toluene (3 mL) at 0 °C for 2 h.

General procedure for the preparation of authentic N-nitroso aldol adduct.⁴

An oven-dried schlenk tube equipped with direct light excluded was charged with (racemic)-BINAP (4 mol%, 0.02 mmol) and AgOTf (10 mol%, 0.05 mmol). THF (2 mL) was added by syringe and the resulting mixture was stirred at room temperature for 20 min. After cooling to -78 °C, nitrosobenzene (1 equiv, 53.6 mg, 0.5 mmol) in ethylen glycol diethyl ether (1 mL) and trimethylsilyloxy diene (1 equiv, 0.5 mmol) was added in this order. The mixture was stirred at -78 °C for 4 h. The reaction mixture was quenched by cooled brine (20 mL) and the aqueous layer was extracted with ether (20 mLx2). The combined organic extracts were washed with brine, dried over Na_2SO_4 with cooling and concentrated under reduced pressure after filtration. The residual crude product in ethylene glycol diethyl ether was chromatographed with cooling on a two-layered column filled with Florisil[®] (upper layer) and silica gel (lower layer) using a mixture of ethyl acetate and hexane as the eluant to give the product.

X-ray crystal data of 3-(4-bromophenyl)-7,7-dimethyl-2-oxa-3-aza-bicyclo [2.2.2] octan-5-one.

Data Collection

An plate-shaped fragment (0.20 x 0.10 x 0.03 mm) was selected under a stereo-microscope while immersed in Fluorolube oil to avoid possible reaction with air. The crystal was removed from the oil using a tapered glass fiber that also served to hold the crystal for data collection. The crystal was mounted and centered on a Bruker SMART APEX system at 102 K. Rotation and still images showed the diffractions to be sharp.

Frames separated in reciprocal space were obtained and provided an orientation matrix and initial cell parameters. Final cell parameters were obtained from the full data set.

A “full sphere” data set was obtained which samples approximately all of reciprocal space to a resolution of 0.75 Å using 0.3° steps in ω using 20 second integration times for each frame. Data collection was made at 102 K. Integration of intensities and refinement of cell parameters were done using SAINT. Absorption corrections were applied using SADABS based on redundant diffractions.

Structure solution and refinement

The space group was determined as $P2_1$ based on systematic absences and intensity statistics. Direct methods were used to locate the Br and most C atoms from the E-map. Repeated difference Fourier maps allowed recognition of all expected Br, C, O, and N atoms. Following anisotropic refinement of all non-H atoms, ideal H atom positions were calculated. Final refinement was anisotropic for Br, O, N and C and isotropic-riding for H atoms. No anomalous bond lengths or thermal parameters were noted. All ORTEP diagrams have been drawn with 50% probability ellipsoids.

Equations of interest:

$$R_{\text{int}} = \sum |F_o|^2 - \langle F_o^2 \rangle / \sum |F_o|^2$$

$$wR2 = [\sum [w (F_o^2 - F_c^2)^2] / \sum [w (F_o^2)^2]]^{1/2}$$

where: $w = 1 / \sigma^2 (F_o^2) + (aP)^2 + bP$;
 reflections; q, a, b, P as defined in [1]

$$R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$$

$$\text{GooF} = S = [\sum [w (F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$$

n = number of independent

p = number of parameters refined.

Table. Crystal and structure refinement of **3-(4-bromophenyl)- 7,7-dimethyl-2-oxa-3-aza-bicyclo[2.2.2] octan-5-one.**

Identification Code	Momy30	
Empirical formula	C ₁₄ H ₁₆ BrNO ₂	
Formula weight	310.19	
Temperature	102 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space Group	P2 ₁	
Unit cell dimensions	$a = 10.981(17)$ Å	$\alpha = 90.0^\circ$
	$b = 6.135(10)$ Å	$\beta = 114.99(2)^\circ$
	$c = 11.014(17)$ Å	$\gamma = 90.0^\circ$
Volume	672.5(18) Å ³	
Z	2	
Density (calculated)	1.532 Mg/m ³	
Absorption coefficient	3.050 mm ⁻¹	
F(000)	316	
Crystal size, color, habit	0.20 x 0.10 x 0.03 mm, clear, plate	
Theta range for data collection	2.04 – 25.02 °	
Index ranges	-13 ≤ h ≤ 13, -7 ≤ k ≤ 7, -13 ≤ l ≤ 13	
Reflections collected	5,613	
Independent reflections	2,354 (R _{int} = 0.0462)	
Reflections with I > 4σ(F _o)	2,145	
Flack parameter	0.0033 (21)	
Absorption correction	SADABS based on redundant diffractions	
Max. and min. transmission	1.0, 0.603	
Refinement method	Full-matrix least squares on F ²	
Weighting scheme	$w = q [\sigma^2 (F_o^2) + (aP)^2 + bP]^{-1}$ where: $P = (F_o^2 + 2F_c^2)/3$, a = 0.0828, b = 0.0, q = 1	
Data / restraints / parameters	2354 / 1 / 165	
Goodness-of-fit on F ²	1.057	
Final R indices [I > 2 sigma(I)]	R1 = 0.0571, wR2 = 0.1286	
R indices (all data)	R1 = 0.0630, wR2 = 0.1315	
Largest diff. peak and hole	1.076, -0.958 eÅ ⁻³	

General procedure for the reaction of cyclohexenone with nitrosobenzene catalyzed by proline or pyrrolidinyI tetrazole (O-Nitroso aldol / Michael Reaction) was reported and the chemical data were described in literature.⁵

General procedure for tandem Diels-Alder reaction

To catalyst (0.40 mol) was added enone (2.0 mmol), nitrosobenzene (4.0 mmol) acetonitrile (4.0 mL). The mixture was allowed to warm to 40°C and was stirred at the same temprature for 15 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography to afford Diels-Alder adduct.

8,8-Dimethyl-3-phenyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one.

Purification by flash column chromatography with elution by (1:9 EtOAc: Hexane) provided as a yellowish oil (64% yield, 99% ee). TLC R_f 0.7 (EtOAc/Hexane, 1:5); $[\alpha]_D^{29} +82.3$ ($c = 1.10$, CHCl_3); FTIR (CDCl_3) ν_{max} 2962, 1743, 1595, 1489, 1028, 992 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.31 (t, $J = 7.4$ Hz, 2 H), 7.09 (d, $J = 8.7$ Hz, 2 H), 7.00 (t, $J = 7.3$ Hz, 1 H), 4.18 - 4.19 (m, 1 H), 3.51 - 3.53 (m, 1 H), 2.71 (dd, $J = 18.7$ Hz, $J = 2.7$ Hz, 1 H), 2.48 (dd, $J = 18.7$ Hz, $J = 3.0$ Hz, 1 H), 2.31 (dd, $J = 14.5$ Hz, $J = 3.9$ Hz, 1 H), 1.81 (dd, $J = 14.5$ Hz, $J = 1.8$ Hz, 1 H), 1.57 (s, 3 H), 1.47 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.1, 149.9, 128.9, 122.4, 116.6, 78.2, 68.4, 39.8, 34.9, 33.1, 28.6, 27.2; MS (CI) Exact Mass Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}^+$): 232.1. Found: 232.1. Enantiometric excess was determined by HPLC with Chiralcel AD-H column (97:3 hexane:2-propanol), 0.8 mL/min; major enantiomer $t_r = 11.1$ min, minor enantiomer $t_r = 10.6$ min. Enantiomer was obtained as a yellowish oil using D-tetrazole catalysis using the same method. (61% yield, 99% ee). $[\alpha]_D^{29} -79.7$ ($c = 0.56$, CHCl_3).

8,12-Dioxaspiro-3-phenyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one.

Purification by flash column chromatography with elution by (1:19 EtOAc: CH_2Cl_2) provided as a yellowish oil (61% yield, 98% ee); TLC R_f 0.6 (EtOAc/ CH_2Cl_2 , 1:19); $[\alpha]_D^{28} -5.4$ ($c = 1.03$, CHCl_3); FTIR (CDCl_3) ν_{max} 2979, 2892, 1747, 1597, 1489, 1227, 1064 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31 (t, $J = 7.4$ Hz, 2 H), 7.13 (d, $J = 8.8$ Hz, 2 H), 7.02 (t, $J = 7.3$ Hz, 1 H) 4.32 (dd, $J = 3.6$ Hz, $J = 2.6$ Hz, 1 H), 4.10 - 4.15 (m, 1 H), 3.97 - 4.04 (m, 3 H), 3.92 (t, $J = 2.9$ Hz, 1 H), 2.91 (dd, $J = 15.2$ Hz, $J = 3.9$ Hz, 1 H), 2.88 (dd, $J = 18.5$ Hz, $J = 2.9$ Hz, 1 H) 2.66 (dd, $J = 18.5$ Hz, $J = 2.9$ Hz, 1 H), 2.28 (dd, $J = 15.2$ Hz, $J = 2.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 204.9, 148.9, 128.8, 122.9, 116.8, 105.5, 77.9, 64.9, 64.8, 64.4, 38.7, 64.5; MS (CI) Exact Mass Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}^+$): 262.1. Found: 262.1. Enantiometric excess was determined by HPLC with Chiralcel AD-H column (90:10 hexane:2-propanol), 1.0mL/min; major enantiomer $t_r = 20.5$ min, minor enantiomer $t_r = 17.3$ min.

7-Phenyl-6-oxa-7-aza-bicyclo[3.2.2]nonan-9-one. Purification by flash column chromatography with elution by (1:1 Hexane: CH_2Cl_2) provided as a yellowish oil (51% yield, 99% ee); TLC R_f 0.7 (Hexane/ CH_2Cl_2 , 1:19); $[\alpha]_D^{29} -186.5$ ($c = 1.12$, CHCl_3); FTIR (CDCl_3) ν_{max} 2946, 1736, 1597, 1489,

1204, 1102, 1038, 734 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31 (t, $J = 7.4$ Hz, 2 H), 7.04 (d, $J = 8.8$ Hz, 2 H), 6.92 (t, $J = 7.4$ Hz, 1 H), 4.60 (br d, $J = 5.8$ Hz, 1 H), 4.36 – 4.39 (m, 1 H), 2.98 (dd, $J = 18.1$ Hz, $J = 5.5$ Hz, 1 H), 2.43 (dd, $J = 18.1$ Hz, $J = 2.1$ Hz, 1 H), 2.07 – 2.16 (m, 3 H), 1.86 – 1.96 (m, 1 H), 1.71–1.82 (m, 1 H), 1.42 – 1.56 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.5, 150.0, 129.0, 121.0, 114.7, 83.6, 56.9, 38.8, 30.9, 29.7, 18.9; MS (CI) Exact Mass Calcd for $\text{C}_{13}\text{H}_{16}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$: 218.1. Found: 218.1. Enantiometric excess was determined by HPLC with Chiralcel AD-H column (90:10 hexane:2-propanol), 1.0mL/min; major enantiomer $t_r = 8.5$ min, minor enantiomer $t_r = 6.9$ min.

3,8,8-Triphenyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one. Purification by flash column chromatography with elution by (1:1 Hexane: CH_2Cl_2) provided as a yellowish crystal (56% yield, 99% ee); TLC R_f 0.7 (CH_2Cl_2); $[\alpha]_D^{30} +288.4$ ($c = 0.97$, CHCl_3); FTIR (CDCl_3) ν_{max} 3058, 2361, 2337, 1743, 1596, 1449, 1394, 1032, 998, 909 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.14–7.45 (m, 15 H), 4.86–4.88 (m, 1 H), 4.41–4.43 (m, 1 H), 3.38 (dd, $J = 15.4$ Hz, $J = 2.6$ Hz, 1 H), 3.11 (dd, $J = 15.4$ Hz, $J = 3.4$ Hz, 1 H), 2.64 (dd, $J = 18.8$ Hz, $J = 3.1$ Hz, 1 H), 1.97 (dd, $J = 18.8$ Hz, $J = 2.8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.5, 149.2, 148.4, 144.1, 129.1, 128.9, 128.3, 127.0, 126.9, 126.8, 126.2, 122.8, 116.5, 76.7, 64.0, 48.3, 37.0, 35.7; MS (CI) Exact Mass Calcd for $\text{C}_{13}\text{H}_{22}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$: 355.2. Found: 355.2. Enantiometric excess was determined by HPLC with Chiralcel AD-H column (95:5 hexane:2-propanol), 1.0mL/min; major enantiomer $t_r = 10.1$ min, minor enantiomer $t_r = 8.8$ min.

3-Phenyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one. Purification by flash column chromatography with elution by (1:4 EtOAc: Hexane) provided as a yellowish oil (34% yield, 99% ee); TLC R_f 0.5 (EtOAc/Hexane 1 : 3); $[\alpha]_D^{27} -216.9$ ($c = 0.6$, CHCl_3); FTIR (CDCl_3) ν_{max} 2965, 1745, 1596, 1488, 1306, 1220, 1174, 986 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31 (t, $J = 7.4$ Hz, 2 H), 7.12 (d, $J = 8.7$ Hz, 2 H), 7.00 (t, $J = 7.3$ Hz, 1 H), 4.19 – 4.22 (m, 2 H), 3.02 (br d, $J = 18.2$ Hz, 1 H), 2.47 (dd, $J = 18.1$ Hz, $J = 3.1$ Hz, 1 H), 2.26 – 2.40 (m, 2 H), 1.91 – 1.99 (m, 1 H), 1.61 – 1.68 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.1, 150.3, 129.0, 122.2, 116.2, 76.9, 56.1, 41.8, 22.4, 21.5; MS (CI) Exact Mass Calcd for $\text{C}_{13}\text{H}_{14}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$: 204.1. Found: 204.1. Enantiometric excess was determined by HPLC with Chiralcel AD-H column (90:10 hexane:2-propanol), 1.0mL/min; major enantiomer $t_r = 23.4$ min, minor enantiomer $t_r = 10.0$ min.

3-(4-Bromo-phenyl)-8,8-dimethyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one. Solvent system was changed to $\text{CH}_2\text{Cl}_2/\text{MeCN}$ 1:1 (6 mL) was used instead of use of CH_2Cl_2 . Purification by flash column chromatography with elution by CH_2Cl_2 provided as a yellowish crystal (50% yield, 99% ee); TLC R_f 0.6 (CH_2Cl_2); $[\alpha]_D^{27} +68.1$ ($c = 2.17$, CHCl_3); FTIR (CDCl_3) ν_{max} 2962, 2871, 1742, 1587, 1485, 1436, 1028, 825 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.33 (d, $J = 8.9$ Hz, 2 H), 6.90 (d, $J = 8.9$ Hz, 2 H), 4.10 – 4.12 (m, 1 H), 3.40 – 3.42 (m, 1 H), 2.57 (dd, $J = 18.7$ Hz, $J = 2.7$ Hz, 1 H), 2.42 (dd, $J = 18.7$ Hz, $J = 2.9$ Hz, 1 H), 2.21 (dd, $J = 14.6$ Hz, $J = 3.9$ Hz, 1 H), 1.73

(dd, $J = 14.5$ Hz, $J = 2.3$ Hz, 1 H) 1.37 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.4, 149.1, 131.8, 118.2, 114.8, 78.3, 68.3, 39.7, 35.0, 33.1, 28.6, 27.2; MS (CI) Exact Mass Calcd for $\text{C}_{14}\text{H}_{17}\text{BrNO}_2$ ($\text{M}+\text{H}$) $^+$: 310.0. Found: 310.0. Enantiometric excess was determined by HPLC with Chiralcel AD-H column (98:2 hexane:2-propanol), 1.0 mL/min; major enantiomer $t_r = 11.3$ min, minor enantiomer $t_r = 15.3$ min.

8,8-Dimethyl-3-*p*-tolyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one.

Purification by flash column chromatography with elution by (1:9 EtOAc: Hexane) provided as a yellowish crystal (46% yield, 98% ee); TLC R_f 0.5 (EtOAc/Hexane 1 : 5); $[\alpha]_D^{27} +44.4$ ($c = 1.32$, CHCl_3); FTIR (CDCl_3) ν_{max} 2961, 1742, 1506, 1028, 994, 817 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.10 (d, $J = 8.1$ Hz, 2 H), 6.98 (d, $J = 8.5$ Hz, 2 H), 4.14 – 4.17 (m, 1 H), 3.42 – 3.45 (m, 1 H), 2.71 (dd, $J = 18.7$ Hz, $J = 2.7$ Hz, 1 H) 2.45 (dd, $J = 18.7$ Hz, $J = 3.0$ Hz, 1 H) 2.30 (dd, $J = 14.4$ Hz, $J = 4.0$ Hz, 1 H), 2.29 (s, 3 H), 1.79 (dd, $J = 14.5$ Hz, $J = 1.8$ Hz, 1 H) 1.47 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.3, 147.6, 132.0, 129.4, 116.8, 78.2, 68.6, 39.9, 34.7, 33.1, 28.6, 27.3, 20.6; $\text{C}_{15}\text{H}_{20}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$: 246.2. Found: 246.1. Enantiometric excess was determined by HPLC with Chiralcel OD-H column x 2 (99:1 hexane:2-propanol), 0.5 mL/min; major enantiomer $t_r = 38.3$ min, minor enantiomer $t_r = 40.7$ min.

3-(3,5-Dimethyl-phenyl)-8,8-dimethyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one.

Purification by flash column chromatography with elution by (1:9 EtOAc: Hexane) provided as a yellowish crystal (52% yield, 98% ee); TLC R_f 0.5 (EtOAc/Hexane 1 : 5); $[\alpha]_D^{27} +70.8$ ($c = 0.67$, CHCl_3); FTIR (CDCl_3) ν_{max} 2961, 2921, 2870, 1742, 1595, 1471, 1028, 1006 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.70 (s, 2 H), 6.64 (s, 1 H), 4.14 – 4.17 (m, 1 H), 3.47 – 3.51 (m, 1 H), 2.72 (dd, $J = 18.7$ Hz, $J = 2.7$ Hz, 1 H) 2.47 (dd, $J = 18.7$ Hz, $J = 3.0$ Hz, 1 H) 2.29 (dd, $J = 14.4$ Hz, $J = 3.9$ Hz, 1 H), 2.29 (s, 6 H), 1.79 (dd, $J = 14.5$ Hz, $J = 2.0$ Hz, 1 H) 1.46 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.4, 150.0, 138.5, 124.2, 114.3, 78.2, 68.2, 39.9, 35.0, 33.1, 28.6, 27.3, 21.5; $\text{C}_{16}\text{H}_{22}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$: 260.2. Found: 260.2. Enantiometric excess was determined by HPLC with Chiralcel AD-H column (97.5:2.5 hexane:2-propanol), 0.4 mL/min; major enantiomer $t_r = 13.7$ min, minor enantiomer $t_r = 12.8$ min.

Preparation of 4-phenoxy nitrosobenzene⁶

To an solution of oxoperoxo(pyridine-2,4-dicboxylato)(hexamethylphosphora triamide)-molybdenum(VI) (7.52 g, 0.020 mol) in CH_2Cl_2 (500 mL) and diethyl ether (500 mL) was added 4-phenoxyaniline (37.0 g, 0.20 mol), and was stirred for an hour at room temperature. H_2O_2 (34 g) was added to the resulting solution and was stirred for 3 h at 45 $^\circ\text{C}$. The resulting muddy reaction mixture was filtered and the filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography with elution by (1:1 hexanes: ethyl acetate) to afford give (38.2 g, 64%) as a green oil.

4-Phenoxyphenyl nitro compound. R_f 0.7 (1:1 hexanes: EtOAc); FTIR (CDCl_3) ν_{max} 1587, 1493, 1351, 1250, 1122, 851, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, J = 8.1 Hz, 2H), 7.14–7.78 (m, 7H).

General procedure for reaction with 4-phenoxyphenyl nitro compound.

To a mixture of pyrrolidinyl tetrazole catalyst (1.11 g, 8.0 mmol) and MeCN (80 mL) was added 4,4-dimethylcyclohexenone (4.96 g, 40 mmol), 4-phenoxyphenyl nitro compound (25.8 g, 80.0 mmol) and AcOH (2.40 g, 40 mmol). The mixture was warmed to 40 °C and was stirred at the same temperature for 15 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography to afford cyclized product (8.28 g, 25.6 mmol) as yellowish oil.

8,8-Dimethyl-3-(4-phenoxyphenyl)-2-oxa-3-azabicyclo[2.2.2]octan-6-one (5). Purification by flash column chromatography with elution by (9:1 hexanes: EtOAc) provided as a yellowish oil (64% yield, 98% ee). TLC R_f 0.7 (5:1 hexanes: EtOAc); $[\alpha]_D^{27}$ +57.3 (c = 1.12, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.29–7.35 (m, 2H), 7.06–7.11 (m, 3H), 6.94–7.02 (m, 4H), –4.19 (m, 1H), 3.43–3.48 (m, 1H), 2.75 (dd, J = 18.7 Hz, J = 2.6 Hz, 1H), 2.49 (dd, J = 18.7 Hz, J = 2.9 Hz, 1H), 2.31 (dd, J = 14.5 Hz, J = 3.9 Hz, 1H), 1.81 (dd, J = 14.5 Hz, J = 2.2 Hz, 1H), 1.47 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.1, 157.9, 152.0, 145.8, 129.6, 122.7, 120.0, 118.2, 118.0, 78.2, 68.7, 39.8, 34.7, 33.1, 28.6, 27.3; Enantiomeric excess was determined by HPLC with Chiralcel AD-H column (97:3 hexane:2-propanol), 0.8 mL/min; major enantiomer t_r = 13.2 min, minor enantiomer t_r = 15.7 min.

General procedure for reduction of 5.

To ice cooled solution of **5** (6.46 g, 20 mmol) in MeOH (65 mL) was added NaBH_4 (832 mg, 22 mmol). The mixture was allowed to warm to room temperature and was stirred for 1 h. The mixture was concentrated under reduced pressure and diluted with EtOAc (130 mL). The organic layer was washed with saturated NH_4Cl aq (65 mL), H_2O (65 mL) and saturated NaCl aq (65 mL), and dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure. The diastereomers were separated through SiO_2 column to afford **6a** (4.88 g, 15 mmol) and **6b** (1.63 g, 5 mmol).

(1R,4R,6R)-8,8-Dimethyl-3-(phenoxyphenyl)-2-oxa-3-azabicyclo[2.2.2]octane-6-ol (6a). TLC R_f 0.6 (1:1 hexanes: EtOAc); $[\alpha]_D^{31}$ +145.9 (c = 1.06, CHCl_3); FTIR (CDCl_3) ν_{max} 2945, 1489, 1232, 1081 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.26–7.30 (m, 2H), 6.92–7.06 (m, 7H), 4.08–4.14 (m, 1H), 4.03–4.06 (m, 1H), 3.22–3.24 (m, 1H), 2.19–2.23 (m, 1H), 1.66–1.90 (m, 3H), 1.35 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.4, 150.5, 147.6, 129.6, 122.4, 120.1, 117.6, 116.7, 73.4, 64.0, 63.7, 33.8, 32.2, 30.0, 28.4, 26.9.

General procedure for transformation to protected amino alcohol (Scheme 7).

To a solution of alcohol **6a** (3.25 g, 10 mmol) in CH_2Cl_2 (40 mL) was added triethylamine (2.63 g, 26 mmol), benzoyl chloride (1.83 g, 13 mmol) and DMAP (61 mg, 0.5 mmol). After the solution was stirred at reflux for 15 h, the mixture was cooled to room temperature. The organic layer was washed with H_2O (40 mL), and dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure and was used for next reaction without further purification.

To this residue was added MeOH (40 mL) and wet 10% Pd/C (325 mg). The vessel was purged with H_2 gas (x3) and was stirred at room temperature for 5 h. Pd/C was filtered off and the filtrate was concentrated under reduced pressure and was used for next reaction without further purification.

To this residue in CH_2Cl_2 (40 mL) was added triethylamine (2.63 g, 26 mmol), benzoyl chloride (1.83 g, 13 mmol) and DMAP (61 mg, 0.5 mmol). After the solution was stirred at reflux for 15 h, the mixture was cooled to room temperature. The organic layer was washed with H_2O (40 mL), and dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure and purified through SiO_2 column to afford **8a** as a yellow oil (3.96 g, 7.4 mmol).

(1S,3S,4S)-3,4-Dibenzoyloxy-6,6-dimethyl-1-(4-phenoxyphenylamino)-cyclohexane (8a). TLC R_f 0.7 (19:1 hexanes: CH_2Cl_2); $[\alpha]_D^{28}$ –46.5 (c = 1.30, CHCl_3); FTIR (CDCl_3) ν_{max} 3413, 2959, 1717, 1507, 1282, 1232, 1111 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.99–8.06 (m, 4H), 7.51–7.56 (m, 2H), 7.39–7.46 (m, 4H), 7.25–7.29 (m, 2H), 6.94–7.02 (m, 1H), 6.91–6.93 (m, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 8.9 Hz, 1H), 5.42–5.55 (m, 2H), 3.64 (br s, 1H), 2.48–3.51 (m, 1H), 2.19–2.27 (m, 2H), 2.03 (dd, J = 14.2 Hz, J = 4.5 Hz, 1H), 1.91 (dd, J = 14.2 Hz, J = 7.9 Hz, 1H), 1.27 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.7, 165.6, 159.0, 147.6, 144.2, 133.1, 133.1, 129.9, 129.6, 129.6, 129.5, 128.4, 128.4, 121.9, 121.3, 117.1, 114.1, 71.3, 71.2, 56.9, 38.8, 30.3, 28.5, 25.2.

General procedure for transformation to protected amino alcohol (Scheme 8).

To a solution **8a** (2.68 g, 5.0 mmol) in MeCN (45 mL) was added H₂O (5 mL) and PhI(OAc)₂ (6.44 g, 20 mmol). The mixture was stirred for 4 h before H₂O (20 mL) and Et₂O (45 mL) was added. The aqueous layer was discarded and the organic layer was washed with saturated Na₂S₂O₈ aq (10 mL) and saturated NaCl aq (10 mL). The organic layer was dried over Na₂SO₄ and was concentrated under reduced pressure. The residue was purified through SiO₂ and used for next reaction.

To the residue was added MeCN (20 mL) and 1 M aqueous HCl (10 mL). The mixture was stirred for 3 h. The mixture was concentrated under reduced pressure and was added saturated Na₂CO₃ aq (20 mL) and EtOAc (40 mL). The aqueous layer was discarded and the organic layer was washed with saturated NaCl aq (20 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was added CH₂Cl₂ (20 mL), NaHCO₃ (1.68 g, 20 mmol) and Ac₂O (10.2 g, 10 mmol). The mixture was stirred for 3 h before H₂O (10 mL) was added. The aqueous layer was discarded and the organic layer was dried over Na₂SO₄ and was concentrated under reduced pressure. The residue was purified through SiO₂ to afford **10a** as a white crystal (1.27 g 3.11 mmol) .

(1S,3S,4S)-1-Acetoxyamino-3,4-dibenzoyloxy-6,6-dimethyl-cyclohexane(**10a**).

$[\alpha]_D^{30}$ -50.8 (c = 1.25, CHCl₃); FTIR (CDCl₃) ν_{max} 3303, 3070, 2964, 1718, 1653, 1541, 1282, 1110, 710 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, *J* = 7.1 Hz, 2H), 7.87 (d, *J* = 7.2 Hz, 2H), 7.26–7.53 (m, 6H), 6.01 (br d, *J* = 9.2 Hz, 1H), 5.41–5.45 (m, 2H), 4.18–4.23 (m, 1H), 2.14–2.17 (m, 2H), 2.06 (s, 3H), 1.96–2.01 (m, 1H), 1.75–1.81 (m, 1H), 1.22 (s, 3H), 1.04 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.7, 166.0, 165.7, 133.2, 133.0, 130.0, 129.6, 129.4, 128.4, 128.3, 71.2, 51.8, 38.6, 34.9, 31.1, 27.3, 25.5, 23.4; MS (CI) Exact Mass Calcd for C₂₄H₂₈NO₅ (M+H)⁺: 410.2. Found: 410.0.

References

- (1) Kilger, R.; Margaretha, P. *Helv. Chim. Acta.* **1983**, *66*, 735-740.
- (2) Maruoka, K.; Itoh, T.; Araki, Y.; Yamamoto, H. *Bull. Chem. Soc. Jpn.*, **1988**, *61*, 2975-2976.
- (3) Ooi, T; Kameda, M.; Keiji, M. *J. Am. Chem. Soc.* **2003**, *125*, 5139-5151.
- (4) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360-5361.
- (5) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962-5963.
- (6) Møller, E. R.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1993**, *115*, 11814-11822.

Optimization Data

Table 1. Reaction of Morpholinodienamine Catalyzed by TADDOL or BINOL^a

1) 30 mol% cat.
toluene, -78 °C
2) 1 N HCl/THF, -78 °C

entry	catalyst	time, h	yield, % ^b	ee, % ^c
1	(4 <i>S</i>)- <i>trans</i> -1-nap TADDOL	12	36	52
2	(<i>S</i>)-BINOL	2	78	28

^aReactions were conducted with 30 mol% of catalyst, 1.0 equiv of nitrosobenzene and 1.5 equiv of dienamine in toluene at -78 °C. ^bIsolated yield. ^cDetermined by HPLC (see the Supporting Information).

Table 2. Effect of amine moieties in **1c** Catalyzed Reaction^a

1) **1c** : Ar = *m*-xyl (30 mol%)
toluene, -78 °C, 2 h
2) 1 N HCl/THF, -78 °C

2a ~ 2c

2a **2b** **2c**

entry	dienamine	yield, % ^b	ee, % ^c
1	2a	57	90
2	2b	49	64
3	2c	23	14

^aReactions were conducted with 30 mol% of catalyst, 1.0 equiv of nitrosobenzene and 1.5 equiv of dienamine in toluene at -78 °C. ^bIsolated yield. ^cDetermined by HPLC (see the Supporting Information).

Table 3. Effect of Catalyst **1c** on Ratio of Cyclized Adduct and N-NA Adduct^a

1)
1c : Ar = *m*-xyl
(30 mol%)
toluene
0 °C
2) 1 N HCl/THF, -78 °C

entry	cat. 1c , mol%	time, h	cyclized adduct (yield, % ^b / ee, % ^c)	aldol adduct (yield, % ^b / ee, % ^c)
1	none	4 h	57 / -	<1 / -
2	100	2 h	4 / -	70 / 21

^aReactions were conducted with or without 30 mol% of catalyst, 1.0 equiv of nitrosobenzene and 1.5 equiv of dienamine in toluene at 0 °C. ^bIsolated yield. ^cDetermined by HPLC (see the Supporting Information).

Table 4. Reaction Optimization in Chiral Enamine Catalysis^a

entry	cat., (mol%)	solvent	conditions	yield, % ^b	ee, % ^c
1	3a (20)	MeCN	40 °C, 15 h	27	99
2	3b (20)	MeCN	40 °C, 15 h	32	99
3	3b (20)	MeCN	40 °C, 20 h	64	99
4	3b (20)	MeCN	r.t., 72 h	42	99
5	3b (10)	MeCN	40 °C, 15 h	27	99
6	3b (20)	DMSO	40 °C, 15 h	7	-
7	3b (20)	MeOH	40 °C, 15 h	<5	-
8	3b (20)	CHCl ₃	40 °C, 15 h	<5	-

^aReactions were conducted with 10 or 20 mol% of catalyst, 1.0 equiv of nitrosobenzene and 0.5 equiv of enone at r.t. or 40 °C. ^bIsolated yield.

^cDetermined by HPLC (see the Supporting Information).

Scheme 1. Proline-catalyzed Reaction of α , β -Unsaturated Ketone

NMR spectrum of cycloadduct in N-NA/Michael Reaction

Current [

NAME

EXPNO

PROCNO

F2 - Acq

Date_

Time_

INSTRUM

PROBHD

PULPROG

TD

SOLVENT

NS

DS

SMH

FIDRES

AQ

RG

DM

DE

TE

D1

P1

SF01

NUC1

PL1

F2 - Processing parameters

SI

SF

WDW

SSB

LB

BB

PC

1D NMR plot parameters

CX

F1P

F1

F2P

F2

PPMCM

HZCM

0.00012

1.00815

1.25451

1.33815

1.37754

1.56581

1.97927

1.98808

2.01447

2.02333

2.31097

2.31920

2.34612

2.35440

2.52317

2.53133

2.57070

2.57891

2.64508

2.65101

2.69260

2.69853

4.14509

4.15343

4.16208

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

ppm

0.00012

1.00815

1.25451

1.33815

1.37754

1.56581

1.97927

1.98808

2.01447

2.02333

2.31097

2.31920

2.34612

2.35440

2.52317

2.53133

2.57070

2.57891

2.64508

2.65101

2.69260

2.69853

4.14509

4.15343

4.16208

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

7.29598

7.31404

7.38573

7.40545

7.42432

7.49295

7.49743

7.51006

7.51448

7.53272

7.55086

7.55382

7.08883

7.09320

7.10605

7.11036

7.26102

Current Data Parameters
 NAME NM5614.3
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20050616
 Time 21.40
 INSTRUM spect
 PROBHD 5 mm Multino
 PULPROG zgpg
 TO 211264
 SOLVENT CDCl3
 NS 494
 DS 1
 SWH 35211.270 Hz
 FIDRES 0.166670 Hz
 AQ 2.9999988 sec
 RG 9195.2
 DM 14.200 usec
 DE 4.50 usec
 TE 300.0 K
 D1 3.0000000 sec
 d11 0.0300000 sec

===== CHANNEL f1 =====

NUC1 13C
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 125.7736214 MHz

===== CHANNEL f2 =====

CPDPRG2 waltz16
 NUC2 1H
 PCPD2 100.00 usec
 PL2 120.00 dB
 PL12 28.00 dB
 SF02 500.1317628 MHz

F2 - Processing parameters
 SI 32768
 SF 125.7577980 MHz
 NDM EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

1D NMR plot parameters
 CX 20.00 cm
 F1P 240.000 ppm
 F1 30181.87 Hz
 F2P -10.000 ppm
 F2 -1257.58 Hz
 PPMCM 12.50000 ppm/cm
 HZCM 1571.97241 Hz/cm

Current NAME EXPNO PROCN

F2 - , Date_ Time_ INSTRUM 5 mm Multinu spect

PROBHD zg PULPROG 32768

TD 32768 SOLVENT CDCl3

NS 1 DS 0

SWH 7507.507 Hz FIDRES 0.229111 Hz

RG 45.3 AQ 2.1823988 sec

DW 66.600 usec DE 4.50 usec

TE 300.0 K

D1 3.00000000 sec

===== CHANNEL f1 =====

NUC1 1H

P1 5.60 usec

PL1 0.00 dB

SFO1 500.1322000 MHz

F2 - Processing parameters

SI 16384

SF 500.1300134 MHz

WDW EM

SSB 0

LB 0.30 Hz

GB 0

PC 1.00

1D NMR plot parameters

CX 20.00 cm

F1P 10.000 ppm

F1 5001.30 Hz

F2P -1.000 ppm

F2 -500.13 Hz

PPMCM 0.55000 ppm/cm

HZCM 275.07150 Hz/cm

Current Data Parameters
 NAME NM5623.1
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20050625
 Time 9.06
 INSTRUM spect
 PROBHD 5 mm Multinu
 PULPROG zgpgc
 TO 211264
 SOLVENT DMS
 NS 977
 DS 1
 SWH 35211.270 Hz
 FIDRES 0.166670 Hz
 AQ 2.9999986 sec
 RG 9195.2
 DM 14.200 usec
 DE 4.50 usec
 TE 300.0 K
 D1 3.00000000 sec
 d11 0.03000000 sec

===== CHANNEL f1 =====

NUC1 13C
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 125.7736214 MHz

===== CHANNEL f2 =====

CPDPRG2 waltz16
 NUC2 1H
 PCPD2 100.00 usec
 PL2 120.00 dB
 PL12 28.00 dB
 SF02 500.1317628 MHz

F2 - Processing parameters

SF 32768
 SF 125.7571948 MHz
 WDM EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

1D NMR plot parameters

CX 20.00 cm
 F1P 220.000 ppm
 F1 27666.71 Hz
 F2P -2515.16 Hz
 F2 12.00000 ppm/cm
 PPMCH 1509.09351 Hz/cm
 HZCM

21.562
 26.359
 28.416
 32.773
 38.566
 40.409
 64.851
 64.851
 76.749
 77.002
 77.257
 81.391
 112.657
 123.835
 138.630
 151.220
 206.742

ppm