CHEMISTRY
AN ASIAN JOURNAL

Supporting Information

Supporting Information

Asymmetric 1,3-Dipolar Cycloadditions of *N*-Benzyl and *N*-Diphenylmethyl Nitrones and α,β-Unsaturated Aldehydes Catalyzed by Bis-Titanium Chiral Lewis Acids

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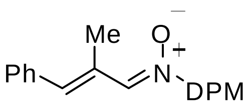
General Information

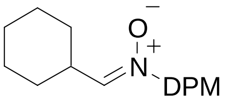
Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet, br = broad, appt = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on a JEOL JNM-FX400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments at 220 nm using 4.6 nm x 25 cm Daicel Chiralcel OD-H and Chiralpak AD-H. High-resolution mass spectra (HRMS) were performed on Applied Biosystems Brucker microTOF or Mariner 8295 API-TOF workstation. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF$_{254}$, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck, 230-400 mesh).

CH_2Cl_2 was purchased from Kanto Chemical Co. Inc. as “Dehydrated” and further purified by passing through neutral alumina under nitrogen atmosphere. Acrolein, methacrolein and crotonaldehyde were freshly distilled before use. Other simple chemicals were purchased and used as such.

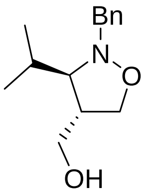
Spectral Data of New Compounds



(*Z*)-*N*-((*E*)-2-Methyl-3-phenylpropenylidene)diphenylmethylamine *N*- Oxide (Table 4, entry 12). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (1H, s, N=C**H**), 7.40-7.33 (14H, m, Ar**H**), 7.25 (1H, m, Ar**H**), 7.08 (1H, s, C=C**H**), 6.25 (1H, s, Ph_2C**H**), 2.17 (3H, s, CC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.2, 134.8, 129.6, 128.6, 128.4, 128.1, 127.5, 127.4, 83.5, 18.1; IR (neat) 3059, 3028, 2358, 2342, 1495, 1449, 1273, 1139, 1031 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{21}NO$: *m/z* 350.1515 ([M + Na]$^+$), found: *m/z* 350.1519 ([M + Na]$^+$).



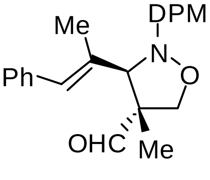
(*Z*)-*N*-Cyclohexylmethylidenediphenylmethylamine *N*-oxide (Table 6, entry 4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (10H, m, Ar**H**), 6.55 (1H, d, *J* = 7.3 Hz, N=C**H**), 6.14 (1H, s, Ph_2C**H**), 3.07 (1H, m, N=CHC**H**), 1.92-1.88 (2H, m, Cy), 1.67 (3H, m, Cy), 1.36 (2H, m, Cy), 1.18 (3H, m, Cy); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 137.0, 128.49, 128.45, 128.2, 81.8, 35.1, 28.9, 26.0, 25.3; IR (neat) 3063, 2920, 2851, 1578, 1495, 1447, 1294, 1258, 1163, 1123, 1103, 1032 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{23}NO$: *m/z* 316.1672 ([M + Na]$^+$), found: *m/z* 316.1672 ([M + Na]$^+$).



(3*R*,4*S*)-2-Benzyl-3-isopropyl-4-hydroxymethylisoxazolidine (Table 2, entry 11). Prepared according to the procedure reported previously[1] with (*Z*)-*N*-isopropylmethylidenebenzylamine *N*-oxide (1.0 mmol, 177 mg) and acrolein (1.5 mmol, 100 μL) over the course of 26 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a colorless oil [43% yield (101 mg), *endo*:*exo* = >20:1, *endo* 54% ee].

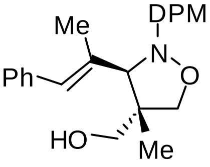
Enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time; 13.6 min (minor) and 16.0 min (major)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.39 (5H, m, Ar**H**), 3.95 (2H, s, PhC**H$_2$**), 3.91 (2H, d, *J* = 5.6 Hz, C**H$_2$**OH), 3.62-3.73 (2H, m, NOC**H$_2$**), 2.53 (1H, m, C**H**CH_2OH), 2.42 (1H, dd, *J* = 4.4, 5.6 Hz, ONC**H**), 1.75 (1H, m, $(CH_3)_2C$**H**), 0.96 (3H, d, *J* = 6.8 Hz, (C**H$_3$**)$_2$CH), 0.95 (H, d, *J* = 6.8 Hz, (C**H$_3$**)$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 128.9, 128.1, 127.1, 73.0, 68.9, 64.8, 61.7, 48.5, 31.3, 20.0, 18.3; IR (neat) 3397, 2955, 2926, 2870, 1497, 1458, 1368, 1211, 1072, 1034, 964 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{14}H_{21}NO_2$: *m/z* 236.1645 ([M + H]$^+$), found: *m/z* 236.1645 ([M + H]$^+$); $[\alpha]^{28}_{\mathrm{D}}$ = –43.2 (*c* = 1.0, CHCl$_3$; 54% ee).



(3*R*,4*R*)-2-Diphenylmethyl-4-formyl-4-methyl-3-((*E*)-1-methyl-2-phenylethenyl)isoxazolidine (Table 2, entry 10). Prepared according to the procedure reported previously[2] with the corresponding nitrone (0.50 mmol, 163.6 mg) and methacrolein (1.5 mmol, 124 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 20:1) to give the cycloadduct as a yellow solid [77% yield (154.0 mg), *endo*:*exo* = >20:1, *endo* 70% ee].

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.51 (1H, s, C**H**O), 7.47 (2H, d, *J* = 7.2 Hz, Ar**H**), 7.40 (2H, d, *J* = 7.2 Hz, Ar**H**), 7.35-7.14 (9H, m, Ar**H**), 7.10 (2H, d, *J* = 7.6 Hz, Ar**H**), 6.44 (1H, br, C=C**H**), 5.11 (1H, s, Ph$_2$C**H**), 4.23 (1H, d, *J* = 9.6 Hz, NOC**H**H), 3.84 (1H, s, ONC**H**), 3.77 (1H, d, *J* = 9.6 Hz, NOCH**H**), 1.69 (3H, br, C=CC**H$_3$**), 1.16 (3H, s, C**H$_3$**); ^{13}C NMR (100 MHz, CDCl$_3$) δ 201.2, 140.7, 137.4, 134.1, 129.7, 128.9, 128.8, 128.6, 128.2, 128.1, 128.0, 127.4, 127.3, 126.5, 73.6, 73.0, 72.2, 61.4, 17.3, 14.0; IR (neat) 3059, 3026, 2858, 2360, 2322, 1724, 1493, 1452, 1053, 1030, 912 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{27}H_{27}NO_2$: *m/z* 420.1934 ([M + Na]$^+$), found: *m/z* 420.1943 ([M + Na]$^+$); $[\alpha]^{27}_{\mathrm{D}}$ = +14.9 (*c* = 1.0, CHCl$_3$; 70% ee).



(3*R*,4*S*)-2-Diphenylmethyl-4-hydroxymethyl-4-methyl-3-((*E*)-1methyl-2-phenylpropenyl)isoxazolidine. Prepared according to the procedure reported previously with the corresponding aldehyde (0.34 mmol, 133.9 mg) and NaBH$_4$ (0.34 mmol, 13 mg) over the course of 30 min. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 6:1) to give the corresponding alcohol as a white solid [92% yield (124.6 mg)].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 16.9 min (minor) and 19.1 min (major)).

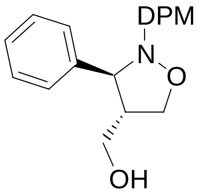
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (2H, d, *J* = 6.8 Hz, Ar**H**), 7.38 (2H, d, *J* = 7.2 Hz, Ar**H**), 7.35-7.09 (11H, m, Ar**H**), 6.30 (1H, br, C=C**H**), 5.08 (1H, s, Ph$_2$C**H**), 3.98 (1H, d, *J* = 8.8

Hz, NOC**H**H), 3.66 (1H, d, *J* = 8.4 Hz, NOCH**H**), 3.48 (2H, br, C**H$_2$**OH), 3.35 (1H, s, ONC**H**), 1.77 (3H, br, C=CC**H$_3$**), 1.02 (3H, s, C**H$_3$**); ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.1, 141.0, 137.8, 136.1, 128.9, 128.8, 128.6, 128.1, 127.99, 127.95, 127.2, 127.1, 126.2, 74.6, 73.8, 69.5, 52.4, 17.4, 16.9; IR (neat) 3420, 3059, 3024, 2968, 2864, 2360, 2330, 1492, 1452, 1043, 1030, 912 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{27}H_{29}NO_2$: *m/z* 422.2090 ([M + Na]$^+$), found: *m/z* 422.2089 ([M + Na]$^+$); $[\alpha]_D^{20}$ = –4.7 (*c* = 1.0, CHCl$_3$; 70% ee).

General Procedure for Asymmetric 1,3-Dipolar Cycloaddition of *N*-Diphenylmethyl Nitrones and Acrolein

To a stirred mixture of Ag_2O (0.10 mmol, 23.2 mg) in CH_2Cl_2 (1.0 mL) was added 1.0 M hexanes solution of ClTi(O*i*Pr)$_3$ (0.20 mmol, 200 μL) at room temperature. After stirring for 5 h at room temperature, a solution of (*S*)-BINOL (0.20 mmol, 57.2 mg) in CH_2Cl_2 (2.0 mL) was added to the mixture, which was then stirred for 2 h at room temperature to afford the dark orange colored solution of (*S*,*S*)-**1a**. To the catalyst solution prepared as described above were added freshly distilled acrolein (1.5 mmol, 100 μL) and a solution of nitrone (1.0 mmol) in CH_2Cl_2 (1.0 mL) dropwise at –40 °C. The reaction mixture was stirred at the same temperature until the completion of the reaction. The mixture was then treated with ethanol solution of $NaBH_4$ (2.0 mmol) and allowed to warm to 0 °C. After stirring for 30 min, the mixture was quenched with aqueous NH_4Cl, filtered to remove insoluble materials and extracted with CH_2Cl_2. The combined organic layers were washed with 1N NaOH to remove (*S*)-BINOL, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate) to give the cycloadduct.

(3*S*,4*S*)-2-Diphenylmethyl-4-hydroxymethyl-3-phenylisoxazolidine (Table 6, entry 1).

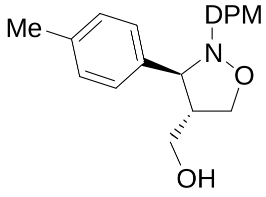


Prepared according to the general procedure with (*Z*)-*N*-benzylidenediphenylmethylamine *N*-oxide (1.0 mmol, 287 mg) and acrolein (1.5 mmol, 100 μL) over the course of 13 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [91 % yield (314 mg), *endo*:*exo* = >20:1, *endo* 97% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 33.1 min (minor) and 37.7 min (major)).

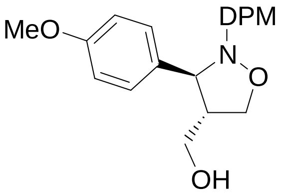
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41-7.03 (15H, m, Ar**H**), 4.93 (1H, s, Ph$_2$C**H**), 4.22 (1H, appt t, *J* = 8.1 Hz, NOC**H**H), 3.90 (1H, dd, *J* = 8.6, 5.4 Hz, NOCH**H**), 3.65 (3H, m, C**H$_2$**OH, ONC**H**), 2.73 (1H, m, C**H**CH$_2$OH); ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.3, 141.0, 140.5, 128.6, 128.13, 128.07, 127.96, 127.8, 127.5, 127.0, 126.9, 126.8, 72.5, 69.7, 68.7, 63.1, 55.8; IR (neat) 3402, 3061, 3026, 2943, 2870, 1738, 1493, 1452, 1366, 1229, 1217, 1074, 1030, 999 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{23}NO_2$: *m/z* 368.1621 ([M + Na]$^+$), found: *m/z* 368.1625 ([M + Na]$^+$); $[\alpha]_D^{27}$ = –53.8 (*c* = 1.0, CHCl$_3$; 97% ee).

(3*S*,4*S*)-2-Diphenylmethyl-4-hydroxymethyl-3-(4-methylphenyl)isoxazolidine (Table 6, entry 2). Prepared according to the general procedure with (*Z*)-*N*-(4-methylbenzylidene)diphenylmethylamine *N*-oxide (1.0 mmol, 301 mg) and acrolein (1.5 mmol, 100 μL) over the course of 12 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [93 % yield (334 mg), *endo*:*exo* = >20:1, *endo* 98% ee].



Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 26.7 min (minor) and 37.1 min (major)).

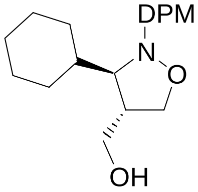
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38-7.01 (14H, m, Ar**H**), 4.90 (1H, s, Ph$_2$C**H**), 4.17 (1H, appt t, *J* = 8.0 Hz, NOC**H**H), 3.84 (1H, dd, *J* = 8.2, 5.6 Hz, NOCH**H**), 3.55 (3H, m, C**H$_2$**OH, ONC**H**), 2.67 (1H, m, C**H**CH$_2$OH), 2.29 (3H, s, ArC**H$_3$**); ^{13}C NMR (100 MHz, CDCl$_3$) δ141.3, 140.2, 138.1, 136.7, 129.0, 128.9, 128.02, 127.96, 127.8, 127.5, 127.1, 126.8, 71.9, 69.3, 68.7, 63.4, 55.6, 21.2; IR (neat) 3395, 3024, 2941, 2868, 1514, 1492, 1452, 1180, 1109, 1076, 1030, 1003 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{25}NO_2$: *m/z* 382.1778 ([M + Na]$^+$), found: *m/z* 382.1784 ([M + Na]$^+$); $[\alpha]_D^{26}$ = –69.2 (*c* = 1.0, CHCl$_3$; 98% ee).



(3*S*,4*S*)-2-Diphenylmethyl-4-hydroxymethyl-3-(4-methoxyphenyl)isoxazolidine (Table 6, entry 3). Prepared according to the general procedure with (*Z*)-*N*-(4-methoxybenzylidene)diphenylmethylamine *N*-oxide (1.0 mmol, 317 mg) in CH_2Cl_2 (5.0 ml) and acrolein (1.5 mmol, 100 μL) over the course of 15 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [99 % yield (371 mg), *endo*:*exo* = 11.2:1, *endo* 98% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 40.5 min (major) and 45.0 min (minor)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.03 (14H, m, Ar**H**), 6.73 (2H, d, *J* = 7.5 Hz, Ar**H**), 4.88 (1H, s, Ph_2C**H**), 4.13 (1H, appt t, *J* = 8.0 Hz, NOC**H**H), 3.80 (1H, dd, *J* = 8.2, 5.8Hz, NOCH**H**), 3.71 (3H, s, OC**H₃**), 3.50 (3H, m, C**H₂**OH, ONC**H**), 2.62 (1H, m, C**H**CH_2OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 141.1, 140.3, 133.0, 128.7, 128.6, 127.93, 127.87, 127.7, 127.0, 126.7, 113.6, 72.0, 69.0, 68.6, 63.0, 55.4, 55.2; IR (neat) 3418, 3061, 3026, 2936, 2870, 1611, 1510, 1452, 1302, 1246, 1173, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{25}NO_3$: *m/z* 376.1907 ([M + Na]$^+$), found: *m/z* 376.1907 ([M + Na]$^+$); $[\alpha]_D^{27}$ = –76.7 (*c* = 1.0, $CHCl_3$; 98% ee).

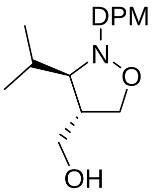


(3*R*,4*S*)-3-Cyclohexyl-2-diphenylmethyl-4-hydroxymethylisoxazolidine (Table 6, entry 4). Prepared according to the general procedure with (*Z*)-*N*-cyclohexylmethylidenediphenylmethylamine *N*-oxide (1.0 mmol, 293 mg) and acrolein (1.5 mmol, 100 μL) over the course of 20 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [99 % yield (351 mg), *endo*:*exo* = >20:1, *endo* 97% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 23.1 min (major) and 24.5 min (minor)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.15 (10H, m, Ar**H**), 5.03 (1H, s, Ph_2C**H**), 3.91 (1H, appt t, *J* = 8.2 Hz, NOC**H**H), 3.85 (1H, appt t, *J* = 7.7 Hz, NOCH**H**), 3.63-3.53 (2H, m, C**H₂**OH), 2.62 (1H, d, *J* = 6.2 Hz, ONC**H**), 2.58 (1H, m, C**H**CH_2OH) 0.73-1.92 (11H, m, Cy); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.3, 128.6, 128.1, 127.9, 127.8, 127.2, 126.7, 72.5, 69.2, 68.4, 64.4, 49.1, 42.3, 30.4, 28.8, 26.6, 26.30, 26.28; IR (neat) 3429, 2922, 2851, 1493, 1450, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{29}NO_2$: *m/z* 374.2091 ([M + Na]$^+$), found: *m/z* 374.2090 ([M + Na]$^+$); $[\alpha]_D^{31}$ = +32.0 (*c* = 1.0, $CHCl_3$; 97% ee).

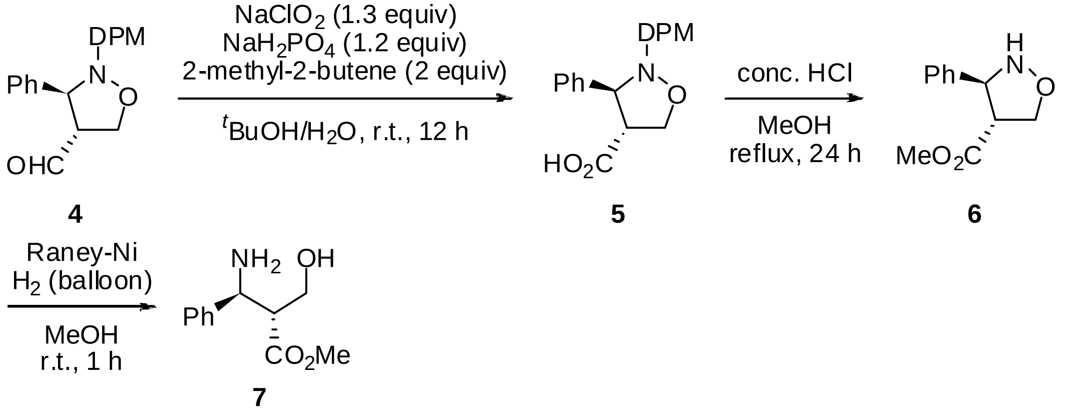
(3*R*,4*S*)-2-Diphenylmethyl-3-isopropyl-4-hydroxymethylisoxazolidine (Table 6, entry 5). Prepared according to the general procedure with (*Z*)-*N*-isopropylmethylidenediphenylmethylamine *N*-oxide (1.0 mmol, 253 mg) and acrolein (1.5 mmol, 100 μL) over the course of 5 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [83% yield (259 mg), *endo*:*exo* = >20:1, *endo* 97% ee].



Enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 40:1, flow rate = 1.0 mL/min, retention time; 21.9 min (minor) and 24.4 min (major)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.16 (10H, m, Ar**H**), 5.05 (1H, s, Ph_2C**H**), 3.97-3.87 (2H, m, NOC$\mathbf{H_2}$), 3.67 (2H, dd, *J* = 12.8, 9.4 Hz, C$\mathbf{H_2}$OH), 2.68 (1H, dd, *J* = 5.8, 3.9 Hz, ONC**H**), 2.58 (1H, m, C**H**CH_2OH), 1.54 (1H, m, $(CH_3)_2C$**H**), 0.86 (3H, d, *J* = 6.8 Hz, (C$\mathbf{H_3}$)$_2$CH), 0.80 (3H, d, *J* = 6.8 Hz, (C$\mathbf{H_3}$)$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.4, 128.7, 128.2, 128.0, 127.8, 127.3, 126.8, 72.7, 69.8, 68.6, 64.7, 48.6, 32.1, 19.9, 18.0; IR (neat) 3431, 2955, 2870, 1493, 1452, 1072, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{25}NO_2$: *m/z* 334.1778 ([M + Na]$^+$), found: *m/z* 334.1774 ([M + Na]$^+$); $[\alpha]_D^{27}$ = +50.7 (*c* = 1.0, $CHCl_3$; 97% ee).

Transformation of the Cycloadduct to β-Amino Acid Ester 7 (Scheme 3)



(3*R*,4*S*)-3-Phenylisoxazolidine-4-carboxylic acid methyl ester 6 (Scheme 3). To a solution of 2-methyl-2-butene (182 μL, 1.72 mmol) and **4** (0.86 mmol, 295 mg), which was isolated from the reaction of *N*-benzylidenediphenylamine *N*-oxide and acrolein without reducing the aldehyde, in *t*BuOH (52 mL) was added aqueous solution of $NaClO_2$ (101 mg, 1.12 mmol) and $NaH_2PO_4 \cdot H_2O$ (1.0 mmol, 138 mg). The reaction mixture was stirred for 12 h at room temperature before the solvent was removed in vacuo. The crude mixture was passed through silica gel columns (eluting with ethyl acetate) to give the carboxylic acid **5** in 91% yield (0.78 mmol, 282 mg).

To a solution of the carboxylic acid **5** (0.20 mmol, 71.9 mg) thus obtained in MeOH (0.60 mL) was added conc. HCl (0.30 mL) and the reaction solution was refluxed for 24 h. The solution was then poured into aqueous $NaHCO_3$ and organic materials were extracted with ethyl acetate. The organic phase was then dried over Na_2SO_4 and concentrated in vacuo. The residue was then purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 4:1) to give **6** as a white solid [50% yield (20.7 mg)].

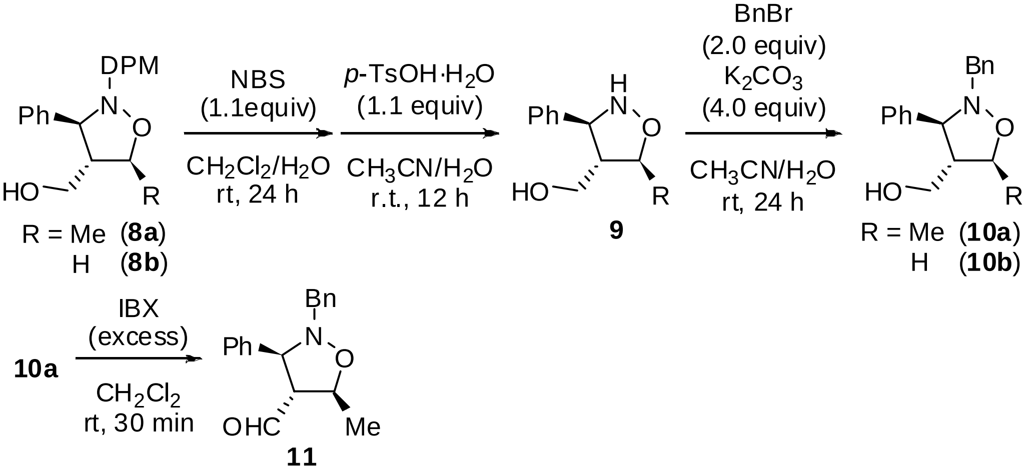
^{1}H NMR ($CDCl_3$) δ 7.42-7.24 (5H, m, Ar**H**), 5.78 (1H, s, N**H**), 4.75 (1H, br, PhC**H**), 4.27 (1H, br, NOC**H**H), 4.11 (1H, br, NOCH**H**), 3.78 (3H, s, C**H**$_3$), 3.51 (1H, m, C**H**CO_2Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 128.8, 127.8, 126.6, 73.7, 67.2, 56.2, 52.5, 29.7; IR (neat) 3219, 2953, 2332, 1730, 1495, 1435, 1368, 1204, 1173, 1074, 1028 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{11}H_{13}NO_3$: *m/z* 230.0788 ([M + Na]$^+$), found: *m/z* 230.0789 ([M + Na]$^+$); $[\alpha]_D^{28}$ = +108.7 (*c* = 1.0, $CHCl_3$).

(2*R*,3*S*)-3-Amino-2-hydroxymethyl-3phenylpropionic acid methyl ester 7 (Scheme 3). To a stirred solution of **6** (0.10 mmol, 20.7 mg) in MeOH was added spatula tip of

Raney-Ni and the reaction flask was then charged with hydrogen gas (balloon). The reaction solution was stirred for 1 h at room temperature and filtered to remove insoluble materials. The filtrate was concentrated under reduced pressure to give the crude material. The residue was then purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH = 10:1) to give **7** as a colorless oil in quantitative yield (0.10 mmol, 21.4 mg).

^{1}H NMR (400 MHz, CD_3OD) δ 7.22-7.12 (5H, m, Ar**H**), 4.04 (1H, d, *J* = 8.5 Hz, C**H**NH_2), 3.79 (2H, dd, *J* = 6.4, 3.0 Hz, C$\mathbf{H_2}$OH), 3.36 (3H, s, OC$\mathbf{H_3}$), 2.80 (1H, m, C**H**CH_2OH); ^{13}C NMR (100 MHz, CD_3OD) δ 174.8, 144.4, 129.4, 128.5, 128.0, 62.5, 57.2, 57.0, 51.9; IR (neat) 3358, 3296, 2951, 1728, 1593, 1454, 1435, 1362, 1265, 1196, 1167, 1032 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{11}H_{15}NO_3$: *m/z* 210.1125 ([M + H]$^+$), found: *m/z* 210.1128 ([M + H]$^+$); $[\alpha]^{28}_{D}$ = +10.9 (*c* = 0.80, CH_3OH).

Determination of the Absolute Configuration of the Cycloadducts



To a solution of **8** (0.2 mmol) in CH_2Cl_2/H_2O (2.0 mL/0.2 mL) was added 1.1 equiv of NBS (0.22 mmol, 39.2 mg), and the reaction solution was stirred at room temperature for 24 h. The reaction mixture was quenched with aqueous $NaHSO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. To the solution of the crude material in CH_3CN/H_2O (2.0 mL/0.2 mL) was added 1.1 equiv of *p*-TsOH·H_2O (0.22 mmol, 41.8 mg) and the reaction solution was stirred at room temperature for 12 h. The reaction mixture was quenched with Et_3N and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 1:1) to give **9**.

To a solution of **9** and 4.0 equiv of K_2CO_3 in CH_3CN/H_2O (1.0 ml/0.1 ml) was added 2.0 equiv of benzyl bromide and the reaction solution was stirred at room temperature for 24 h. The reaction mixture was quenched with aqueous NH_4Cl and extracted with AcOEt. The combined oraganic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 4:1) to give **10**.

(3*S*,4*S*)-2-Benzyl-4-hydroxymethyl-3-phenylisoxazolidine (10b).

$[\alpha]_D^{29}$ = –97.5 (*c* = 1.0, $CHCl_3$; 97% ee); Lit. $[\alpha]_D^{31}$ = –84.9 (*c* = 1.0, $CHCl_3$; 93% ee) for (3*S*,4*S*)-**10b**.[1]

To a solution of **10a** (19.1 mg, 0.070 mmol) in CH_2Cl_2 (1.0 ml) was added excess amount of IBX and the reaction mixture was stirred at room temperature for 30 min. The mixture was quenched with aqueous $NaHSO_3$ and $NaHCO_3$ and extracted with CH_2Cl_2. The combined oraganic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 15:1) to give **11** as a colorless oil in 54% yield (0.038 mmol, 10.6 mg).

(3*S*,4*R*,5*S*)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine (11).

$[\alpha]_D^{29}$ = –75.7 (*c* = 1.0, $CHCl_3$; 87% ee); Lit. $[\alpha]_D$ = +82.5 (*c* = 1.0, $CHCl_3$; 94% ee) for (3*R*,4*S*,5*R*)-**11**.[3]

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