Supporting Information

Highly Diastereoselective Multicomponent Synthesis of Unsymmetrical Imidazolines

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Supplemental:

A) Synthesis of 2-oxazolin-5-ones: A solution of benzoyl amino acid (2 mmol.) and EDCI.HCl (2 mmol.) in dichloromethane (20 mL) was stirred at 0°C for 1h for racemic compounds, 15 min for optically active compounds. The reaction mixture was washed successively with cold (containing ice) water, aqueous NaHCO₃, and water (10mL each) The solution was dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated to dryness *in vacuo* giving the oxazolones as solids or oils.

B) General Procedure for synthesis of Imidazoline-4-carboxylic acids. A solution of aldehyde (0.57 mmol) and amine (0.57 mmol) in dry toluene (10 mL) was refluxed under nitrogen for 2 h. The solvent was evaporated under reduced pressure and the imine redissolved in dichloromethane (10 mL). To the solution was added oxazolone (0.57 mmol) and chlorotrimethylsilane (0.74 mmol) and the mixture was refluxed under nitrogen for 6-10 h and then stirred overnight at room temperature. The product was either precipitated out from 1:1 dichloromethane/ hexane or isolated after silica gel chromatography with 4:1 ethyl acetate /methanol.

Compound 1. dl-(3S, 4S)-1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid. A solution of benzaldehyde (0.06 g, 0.57 mmol), benzylamine (0.061 g, 0.57 mmol) in dry dichloromethane (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4H-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at room temperature. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated out as a white solid using a 1:1 dichloromethane/ hexanes mixture (0.155 g, 74 %). ¹H NMR (300 MHz) (DMSO-*d*₆): δ 1.8 (3H, s), 4.05 (1H, d, J = 15Hz), 4.95 (1H, d, J = 14.8 Hz), 5.05 (1H, s), 7.05 (2H, s), 7.25-7.54 (8H, m), 7.74 (2H, t, J = 7.2Hz), 7.83 (1H, t, J = 6.9Hz), 8.0 (2H, d, J = 8.4Hz); ¹³C NMR (75 MHz) (DMSO-*d*₆): δ 25.2, 48.8, 70.4, 73.3, 122.3, 127.8, 128.3, 128.5, 128.9, 129.1, 129.3, 129.6, 129.7, 132.3, 133.2, 134, 166.1, 169.5; IR (neat): 3350cm⁻¹, 1738 cm⁻¹; HRMS (EI): calculated for C₂₄H₂₂N₂O₂ [M-H]⁺ 369.1603, found [M-H]⁺ 369.1610; M. P.: decomposes at 185-190 °C.

Compound 2. dl-(3S, 4S)-1-Benzyl-5-(4-methoxyphenyl)-4-methyl-2-phenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid. A solution of p-anisaldehyde (0.077 g, 0.57 mmol), benzylamine (0.061 g, 0.57 mmol) in dry dichloromethane (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4H-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at room temperature. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated out as a white solid using a 1:1 dichloromethane/ hexanes mixture (0.180 g, 78 %). ¹H NMR (300 MHz) (CDCl₃ + 2 drops DMSO-*d*₆):

δ 1.8 (3H, s), 3.8 (3H, s), 3.95 (1H, d, J = 15.3Hz), 4.5 (1H, s), 4.9 (1H, d, J = 15Hz), 6.83-6.92 (4H, m), 7.08-7.19 (3H, m), 7.3-7.4 (3H, dd, J₁ = 5.1Hz, J₂ = 1.8Hz), 7.54-7.62 (2H, t, J = 7.2Hz), 762-7.68 (1H, t, J = 7.2Hz), 7.9 (2H, d, J = 6.9 Hz); ¹³C NMR (75 MHz) (CDCl₃): δ 25.3, 48.8, 55.6, 70.9, 74.1, 115.2, 122.2, 123, 125.5, 127.9, 128.4, 129.2, 129.3, 129.6, 129.9, 132.8, 134.2, 161.1, 166.3, 168.4; IR (neat): 3388 cm⁻¹, 1738 cm⁻¹; HRMS (EI): calculated for C₂₅H₂₄N₂O₃ [M-H]⁺ 397.1709, found [M-H]⁺ 399.1717; M. P.: decomposes at 205-208 °C.

Compound 3. dl-(3S, 4S)-1-Benzyl-4-methyl-2-phenyl-5-pyridin-4-yl-4,5-dihydro-1H-imidazole-4-carboxylic acid. A solution of pyridin-4-carboxylaldehyde (0.061 g, 0.57 mmol), benzylamine (0.061 g, 0.57 mmol) in dry dichloromethane (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4H-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at room temperature. The reaction mixture was evaporated to dryness under vacuum. The product was isolated using 4:1 ethyl acetate /methanol as an off-white solid (0.161 g, 76 %). ¹H NMR (300 MHz) (DMSO-*d*₆): δ 1.8 (3H, s), 4.24 (1H, d, J = 15.9Hz), 4.9 (1H, d, J = 14.8 Hz), 5.15 (1H, s), 7.0-7.15 (2H, m), 7.25-7.35 (3H, m), 7.4-7.5 (2H, m), 7.7-7.9 (3H, m), -7.95-8.05 (2H, m), 8.6-8.7 (2H, m); ¹³C NMR (75 MHz) (DMSO-*d*₆): δ 25.1, 49.1, 70.6, 71.7, 122.1, 123, 127.9, 128.4, 128.8, 129.2, 129.4, 132.8, 133.9, 141.4, 149.8, 166.5, 169.05; IR (neat): 3400cm⁻¹, 1746 cm⁻¹; HRMS (EI): calculated for C₂₃H₂₁N₃O₂ [M-H]⁺ 370.1556, found [M-H]⁺ 370.1556; M. P.: decomposes at 185-190 °C.

Compound 4. dl-(3S, 4S)-1-(4-Fluorophenyl)-4-methyl-2-phenyl-4,5-dihydro-1H-imidazole-4,5-dicarboxylic acid 5-ethyl ester. A solution of ethyl glyoxalate (0.058 g, 0.57 mmol) as 50 % solution in toluene (1.03 g/mL), 4-fluoroaniline (0.063 g, 0.57 mmol) in dry dichloromethane (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4H-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at room temperature. The reaction mixture was evaporated to dryness under vacuum. The product was purified by silica-gel column chromatography using 4:1 ethyl acetate / methanol, to yield a white solid (0.152 g, 72 %). ¹H NMR (300 MHz) (CD₃OD): δ 1.2 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 4.9 (2H, dq, J₁ = 7.2 Hz, J₂ = 2.1 Hz), 5.48 (1H, s), 7.1-7.8 (9H, m); ¹³C NMR (75 MHz) (CD₃OD): δ 169.9, 166.2, 164.0, 162.1, 134.4, 131.5, 129.7, 129.6, 129.5, 129.3, 121.8, 116.9, 116.7, 75.1, 69.1, 62.9, 24.2, 12.8; IR (neat): 3450 cm⁻¹, 1743 cm⁻¹; HRMS (EI): calculated for C₂₀H₁₉FN₂O₄ [M-H]⁺ 369.1251, and observed [M-H]⁺ 369.1255; M. P.: decomposes at 190-193 °C.

Compound 5. dl-(3S, 4S)-1-(2-Ethoxycarbonyl-ethyl)-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid. A solution of 3-(benzylidene-amino)-propionic acid ethyl ester (1.4 g, 6.8 mmol) in dry methylene chloride (60 mL) was added to a well stirred solution of 2-phenyl-4-dimethyl-4H-oxazolin-5-one (1.0 g, 5.7 mmol) and TMSCl (1 mL, 6.8 mmol) in dry dichloromethane (80 mL) and the mixture was refluxed under nitrogen for 10 h and then stirred overnight at room temperature. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated out as a white solid using a 1:1 dichloromethane/ hexanes mixture (1.08 g, 51.4 %). ¹H NMR (500 MHz) (CD₃OD): δ 1.17 (t, J = 7.5, 3H), 1.9 (s, 3H), 2.47-2.52 (m, 1H), 2.52-2.71 (m, 1H), 3.34-3.39 (m, 1H), 3.40-4.09 (m, 3H), 5.42 (s, 1H), 7.46-7.49 (m, 5H), 7.72-7.87 (m, 5H). ¹³C NMR (100 MHz) (CD₃OD): δ 13.35, 24.87, 30.64, 41.64, 61.00, 70.94, 73.51, 122.77, 128.99, 129.21, 129.80, 130.10, 132.78, 134.09, 167.32, 169.81, 170.9. IR (neat): 3481cm⁻¹, 1743 cm⁻¹; MS (EI): calculated for C₂₂H₂₄N₂O₄ (m/z) 380.44 observed m/z = 380.7. M. P.: decomposes at 218-220 °C.

Compound 7. dl-(3S, 4S)-1-Methoxycarbonylmethyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid. A solution of (benzylidene-amino)-acetic acid methyl ester (0.34 g, 1.8 mmol) in dry methylene chloride (20 mL) was added to a well stirred solution of 2-phenyl-4-methyl-4H-oxazolin-5-one (0.5 g, 2.85 mmol) and TMSCl (0.37 g, 3.42 mmol) in dry dichloromethane (50 mL) and the mixture was refluxed under nitrogen for 10 h and then stirred overnight at room temperature. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated out as a white solid using a 1:1 dichloromethane/ hexanes mixture (0.70 g, 70 %). ¹H NMR (300 MHz) (CD₃OD): δ 1.99 (3H, s), 3.67 (3H, s), 3.96 (1H, d, J = 18.3 Hz), 4.53 (1H, d, J = 18.3 Hz), 5.39 (1H, s), 7.47-7.50 (5H, m), 7.74-7.87 (5H, m). ¹³C NMR (75 MHz) (CD₃OD): δ 24.23, 52.09, 70.83, 75.38, 121.84, 128.26, 128.69, 129.52, 129.75, 131.78, 134.02, 167.59, 168.62, 169.19; IR (neat): 3468 cm⁻¹, 1747 cm⁻¹; MS (EI): calculated for C₂₀H₂₀N₂O₄ (m/z) 352.14 observed m/z = 353.2; M. P.: decomposes at 215-217 °C.

Compound 8. dl-(3S, 4S)-1-(4-Fluorophenyl)-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid. A solution of benzaldehyde (0.060 g, 0.57 mmol), 4-fluoroaniline (0.063 g, 0.57 mmol) in dry dichloromethane (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4H-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at room temperature. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated out as a white solid using a 1:1 dichloromethane/ hexanes mixture (0.160 g, 74 %). ¹H NMR (300 MHz) (DMSO-*d*₆): δ 1.98 (3H, s), 5.98 (1H, s), 7.05-7.65 (14H, m); ¹³C NMR (75 MHz) (DMSO-*d*₆): δ 25.2, 71.2, 77.9, 116.9, 117, 117.1, 117.3, 123, 125.1, 125.3, 129.3, 129.4, 129.6, 130.1, 130.3, 130.4, 130.5, 132.5, 133.3, 134.5, 160.4, 163.7, 165.3, 170.4; IR (neat): 3450 cm⁻¹, 1744 cm⁻¹. HRMS (EI): calculated for C₂₃H₁₉FN₂O₂ [M-H]⁺ 373.1352, found [M-H]⁺ 373.1359; M. P.: decomposes at 230-232 °C.

Compound 9. 1-Benzyl-5-(4-methoxy-phenyl)-2,4-dimethyl-4,5-dihydro-1H-imidazole-4-carboxylic acid. A solution of p-anisaldehyde (1.4 g, 10.4 mmol), benzylamine (1.11 g, 10.4 mmol) in dry dichloromethane (150 mL) was refluxed under nitrogen for 2 h. 2, 4-dimethyl-4H-oxazolin-5-one (1 g, 8.7 mmol) and chlorotrimethylsilane (1.22 g, 11.3 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at room temperature. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated out as a white solid using a 1:1 dichloromethane/ hexanes mixture (1.9 g, 65 %). ¹H NMR (300 MHz) (CDCl₃): δ 1.13 (3H, s), 2.43 (3H, s), 3.83 (3H, s), 4.17 (1H, d, J = 15.9 Hz), 4.57 (1H, d, J = 15.9 Hz), 5.8 (1H, s) 6.92 (2H, d, J = 8 Hz), 7.05 (2H, d, J = 8 Hz) 7.2-7.4 (5H, m); ¹³C NMR (75 MHz) (CDCl₃): δ 12.3, 21.9, 47.8, 55.2, 70.4, 114.3, 125.2, 126.9, 128.5, 129.3, 133.3, 159.9, 163.2, 174.8; IR (neat): 3388 cm⁻¹, 1738 cm⁻¹; HRMS (EI): calculated for C₂₀H₂₂N₂O₃ [M-H]⁺ (m/z) = 337.1552, found (m/z) 337.1548. M.P.: decomposes at 218-220 °C

Compound 10. dl-(3S, 4S)-1-Benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid. A solution of benzaldehyde (0.6 g, 5.7 mmol), benzylamine (0.61 g, 5.7 mmol) in dry dichloromethane (120 mL) was refluxed under nitrogen for 2 h. 2,4-Diphenyl-4H-oxazolin-5-one (1.35 g, 5.7 mmol) and chlorotrimethylsilane (0.8 g, 7.4 mmol) were added and the mixture

was refluxed under nitrogen for 6 h and then stirred overnight at room temperature. The product was purified by silica-gel column chromatography with 1:5 ethanol/ ethyl acetate to afford 2.1 g of the product in 65 % yield as an off-white solid. ¹H NMR (300 MHz) (CDCl₃): δ 3.8 (1H, d, J = 15.6 Hz), 4.62 (1H, d, J = 15.6 Hz), 4.98 (1H, s), 6.58 (2H, d, J = 8.1 Hz), 7.05-7.65 (16H, m), 7.9 (2H, d, J = 7.2 Hz); ¹³C NMR (75 MHz) (CDCl₃): δ 29.7, 48.3, 75.6, 79.1, 123.1, 125.7, 126.7, 127.3, 127.4, 127.9, 128.1, 128.2, 128.8, 128.9, 129, 129.3, 132.9, 133.8, 136, 143.1, 164.8, 168.1; IR (neat): 3400 cm⁻¹ (very broad), 1738 cm⁻¹; HRMS (EI): calculated for C₂₉H₂₄N₂O₂ [(M-H)-CO₂]⁺ 387.1526 and observed [(M-H)-CO₂]⁺ 387.1539; M. P.: decomposes at 153-155 °C.

Compound 11. dl-(3S, 4S)-1-Benzyl-4-(1H-indol-3-ylmethyl)-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid. A solution of benzaldehyde (0.6 g, 5.7 mmol), benzylamine (0.61 g, 5.7 mmol) in dry dichloromethane (120 mL) was refluxed under nitrogen for 2 h. 4-(1H-Indol-3-ylmethyl)-2-phenyl-4H-oxazol-5-one (1.65 g, 5.7 mmol) and chlorotrimethylsilane (0.8 g, 7.4 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at room temperature. The product was purified by silica-gel column chromatography with 1:5 ethanol / ethyl acetate to afford 3.1 g of product in 68 % yield as an off-white solid. ¹H NMR (300 MHz) (DMSO-*d*₆): δ 3.95 (1H, d, J = 16.2 Hz), 4.6 (1H, d, J = 16.2 Hz), 5.25 (1H, s), 6.1 (2H, d, J = 7.8 Hz), 6.9-7.3 (5H, m), 7.3-8.0 (15H, m); ¹³C NMR (75 MHz) (DMSO-*d*₆): δ 169.6, 166, 136.5, 133.7, 132.5, 132.3, 129.7, 129.4, 128.9, 128.7, 128.6, 127.9, 127.8, 126.7, 126.6, 122.7, 121.4, 119, 111, 105.8, 74.4, 70.4, 48.5, 32.3; IR (neat): 3420 cm⁻¹ (very broad), 1741 cm⁻¹; HRMS (EI): calculated for C₃₂H₂₇N₃O₂ [M-H]⁺ 484.2025 and observed [M-H]⁺ 484.2011; M. P.: decomposes at >250 °C.

Compound 12. 1-Benzyl-4-(2-methoxycarbonyl-ethyl)-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid. A solution of benzaldehyde (0.252 g, 2.4 mmol), benzylamine (0.258 g, 2.4 mmol) in dry dichloromethane (100 mL) was refluxed under nitrogen for 2 h. 3-(5-Oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-propionic acid methyl ester (0.5 g, 2 mmol) and chlorotrimethylsilane (0.282 g, 2.6 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at room temperature. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated out as a white solid using a 1:1 dichloromethane/ hexanes mixture (0.54 g, 60 %). ¹H NMR (300 MHz) (CDCl₃): δ 2.05-2.25 (2H, m), 2.3-2.5 (2H, m), 3.55 (3H, s), 4.38 (2H, ddd, J₁ = 4 Hz, J₂ = 9 Hz, J₃ = 25 Hz), 4.86 (1H, q, J = 3.3), 7.1-7.6 (12H, m), 7.7-7.9 (4H, m); ¹³C NMR (75 MHz) (CDCl₃): δ 27.6, 30.1, 43.3, 51.6, 52.7, 127.1, 127.2, 127.3, 128.2, 128.3, 131.5, 131.6, 133.3, 137.8, 167.5, 171.4, 173.6; IR (neat): 1734 cm⁻¹, 1653 cm⁻¹; MS (EI): calculated for C₂₄H₂₂N₂O₂ (m/z) 442.5, found (m/z) 443. M.P.: 110-112 °C

CRYSTAL STRUCTURE:
Compound 7. HCl

Figure 1 supplemental. Crystal data and structure refinement compound 7

Identification code	tepe03
Empirical formula	C20 H22 Cl N2 O4
Formula weight	389.85
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 8.2919(17) Å b = 12.738(3) Å c = 18.178(4) Å alpha = 90 deg. beta = 90.33(3) deg. gamma = 90 deg.
Volume	1920.1(7) Å ³
Z	4
Density (calculated)	1.349 Mg/m ³
Absorption coefficient	0.227 mm ⁻¹
F(000)	820
Crystal size	0.4 x 0.4 x 0.2 mm
Theta range for data collection	1.95 to 28.17 deg.
Index ranges	-10<=h<=9, -16<=k<=16, -23<=l<=20
Reflections collected / unique	11721 / 4459 [R(int) = 0.0182]
Completeness to theta = 28.17	94.7%
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4459 / 0 / 332
Goodness-of-fit on F ²	0.844
Final R indices [I>2sigma(I)]	R1 = 0.0337, wR2 = 0.1016
R indices (all data)	R1 = 0.0445, wR2 = 0.1099

Largest diff. peak and hole 0.325 and -0.224
Spectral data:

Compound 1.

^1H NMR (DMSO- d_6):

^{13}C NMR (DMSO- d_6):

Compound 2.

^1H NMR (CDCl_3 + 2 drops $\text{DMSO}-d_6$):

^{13}C NMR (CDCl_3):

Compound 3.

^1H NMR (DMSO- d_6):

^{13}C NMR (DMSO- d_6):

Compound 4.

^1H NMR (CD_3OD):

^{13}C NMR (CD_3OD):

NOESY-1D (CD_3OD):

Compound 5.

¹H NMR (CD₃OD)

JK-1-215-H

Pulse Sequence: s2pul

¹³C NMR (CD₃OD)

JX-1-216-C
Pulse Sequence: s2pul

Compound 7:

¹H NMR (CD₃OD):

¹³C NMR (CD₃OD):

Compound 8.

^1H NMR (DMSO- d_6):

^{13}C NMR (DMSO- d_6):

Compound 9.

¹H NMR (CDCl₃)

¹³C NMR (CDCl₃)

1-sp-dimethyl-pmethoxyimidazoline-C

Pulse Sequence: s2pul

1-SP-189-C.

Compound 10.

¹H NMR (CDCl₃):

^{13}C NMR (CDCl_3):

Compound 11.

^1H NMR ($\text{DMSO}-d_6$):

^{13}C NMR (CDCl₃)