Synthesis and Application of Recyclable Ionic Liquid-Supported Imidazolidinone Catalyst in Enantioselective 1,3-Dipolar Cycloaddition

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General methods

All nitrones were prepared according to previously reported methods. All α,β-unsaturated aldehydes were purchased from chemical companies and used directly without further purification.

For HPLC analysis of the enantioselectivity of the products, the corresponding racemic isoxazolidine compounds were synthesized by using InBr₃ as catalyst in CH₂Cl₂.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with acidic solution of ceric molybdate or ethanol solution of ninhydride.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions.

High Resolution Mass (HRMS) spectra were obtained using Finnigan MAT95XP GC/HRMS (Thermo Electron Corporation).

Proton nuclear magnetic resonance spectra (¹H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 400 spectrophotometer (CDCl₃ as solvent). Chemical shifts for ¹H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-d (δ 7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (¹³C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). The proportion of diastereomers was determined from the integration of ¹H NMR and/or ¹³C NMR spectra of crude reaction product.
**Synthetic procedure to chiral imidazolidinone catalyst I-III**

**Step 1.** Boc-protection of L-phenylalanine $^1$

![Chemical structure of Boc-protection of L-phenylalanine]

A 250 mL round-bottomed flask was charged with THF (60 mL), H$_2$O (30 mL), and L-phenylalanine $^1$ (30 mmol, 4.96 g) at room temperature. Di-tert-butyl dicarbonate (33 mmol, 7.2 g) was added to the reaction mixture followed by 10% aq. NaOH (37.5 mmol, 1.5 g in 13.5 mL water) and the reaction mixture was stirred at room temperature overnight. Then THF was removed in vacuo and CH$_2$Cl$_2$ (150 mL) was added to the reaction flask. 10% aq. HCl was added dropwise to the solution with stirring until the precipitate ceased forming at around pH = 4. The organic layer was separated from the aqueous media, washed with brine, dried with anhydrous MgSO$_4$ and concentrated in vacuo to give ($S$)-2-(tert-butoxycarbonylamino)-3-phenylpropanoic acid $^2$ in quantitative yield; it was used directly in next step without further purification.

**Step 2.** HOBT/EDC$^3$- or DCC$^4$-mediated coupling of 2 and 3

![Chemical structure of HOBT/EDC-mediated coupling]

To a solution of ($S$)-2-(tert-butoxycarbonylamino)-3-phenylpropanoic acid $^2$ (15 mmol, 3.98 g), $N$-(3-aminopropyl)imidazole $^3$ (22.5 mmol, 2.82 g) and HOBT (24 mmol, 3.24 g) in THF (50 mL) was added EDC.HCl (18 mmol, 3.49 g). The reaction was stirred at room temperature for 2 hours then concentrated in vacuo. Water was added to the residue and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with aq. HCl (1 M), saturated NaHCO$_3$, and brine sequentially. It was further dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to give a residue. It was purified by silica gel column chromatography using ethyl acetate and hexane as eluant to give ($S$)-tert-butyl 1-((1H-imidazol-1-yl)methylamino)-1-oxo-3-phenylpropan-2-ylcarbamate $^4$ in 82% yield.

![Chemical structure of DCC-mediated coupling]

A two-necked flask was charged with ($S$)-2-(tert-butoxycarbonylamino)-3-phenylpropanoic acid $^2$ (15 mmol, 3.98 g), $N$-(3-aminopropyl)imidazole $^3$ (22.5 mmol, 2.82 g) and anhydrous CH$_2$Cl$_2$ (50 mL) under nitrogen atmosphere. The reaction mixture was cooled to 0 °C in an ice-water bath, followed by dropwise addition of DCC (30 mmol, $c$ = 1.0 M in CH$_2$Cl$_2$), then it was warmed to room temperature and stirred for overnight. After reaction, the precipitate was filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using ethyl acetate and hexane as eluant to give ($S$)-tert-butyl 1-((1H-imidazol-1-yl)methylamino)-1-oxo-3-phenylpropan-2-ylcarbamate $^4$ in 75% yield.
yl)methylamino)-1-oxo-3-phenylpropan-2-ylcarbamate 4 in 75% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.40 (s, 9H), 1.81-1.88 (m, 2H), 3.03 (d, $J$ = 7.07 Hz, 2H), 3.08-3.21 (m, 2H), 3.74-3.85 (m, 2H), 4.29 (q, $J$ = 7.37 Hz, 1H), 5.23 (s, 1H), 6.50 (t, $J$ = 5.41 Hz, 1H), 6.87 (s, 1H), 7.02 (s, 1H), 7.20-7.31 (m, 5H), 7.41 (s, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.0 (C), 155.5 (C), 136.9 (CH), 136.6 (C), 129.1 (CH x 2), 128.5 (CH), 128.3 (CH x 2), 128.6 (CH), 118.8 (CH), 79.9 (C), 55.7 (CH), 43.9 (CH$_2$), 38.6 (CH$_2$), 35.9 (CH$_2$), 30.4 (CH$_2$), 28.0 (CH$_3$ x 3) ppm. HRMS (ESI, m/z): [M+H$^+$], calcd. for C$_{20}$H$_{29}$N$_4$O$_3$: 373.2240, found: 373.2227.

**Step 3. CF$_3$COOH-mediated cleavage of Boc-protecting group in substrate 4**

(S)-Tert-Butyl 1-((1H-imidazol-1-yl)methylamino)-1-oxo-3-phenylpropan-2-ylcarbamate 4 (20 mmol, 7.45 g) was dissolved in trifluoroacetic acid (160 mmol, 18.24 g) and stirred at room temperature for 2 days. After reaction, excess trifluoroacetic acid was neutralized by dropwise addition of saturated aq. Na$_2$CO$_3$ until pH = 10. Then it was extracted with CH$_2$Cl$_2$ (50 mL x 3). The combined organic layer was dried with anhydrous MgSO$_4$ and concentrated in vacuo to give crude product. It was further purified by silica gel column chromatography using dichloromethane and methanol as eluant to give (S)-N-((1H-imidazol-1-yl)methyl)-2-amino-3-phenylpropanamide 5 in 64% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.87-1.94 (m, 2H), 2.05 (brs, 2H), 2.75 (dd, $J$ = 13.56, 8.62 Hz, 1H), 3.15 (dd, $J$ = 13.56, 4.69 Hz, 1H), 3.22 (q, $J$ = 6.41 Hz, 2H), 3.58 (dd, $J$ = 8.48, 4.80 Hz, 1H), 3.86 (t, $J$ = 6.92 Hz, 2H), 6.92 (s, 1H), 6.98 (s, 1H), 7.18-7.30 (m, 5H), 7.42 (s, 1H), 7.81 (t, $J$ = 5.60 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 174.3 (C), 137.3 (CH), 136.6 (C), 128.9 (CH x 2), 128.7 (CH), 128.1 (CH x 2), 126.3 (CH), 118.6 (CH), 55.9 (CH), 44.0 (CH$_2$), 40.7 (CH$_2$), 35.7 (CH$_2$), 30.5 (CH$_2$) ppm. HRMS (ESI, m/z): [M+H$^+$], calcd. for C$_{15}$H$_{21}$N$_4$O: 273.1715, found: 273.1713.

**Step 4. Ring-closure of substrate 5 with acetone under acid catalysis**

(S)-N-((1H-Imidazol-1-yl)methyl)-2-amino-3-phenylpropanamide 5 (10 mmol, 2.72 g) was dissolved in methanol (60 mL), followed by addition of acetone (30 mL) and CSA (2 mmol, 0.46 g). The reaction was stirred under refluxing for overnight. After reaction, the solvent was removed under vacuo and the residue was dissolved in CH$_2$Cl$_2$, washed with saturated NaHCO$_3$ and brine, and dried over MgSO$_4$. After removal of organic solvent under vacuo, the residue was purified by silica gel column chromatography using dichloromethane and methanol as eluant to give (S)-3-((1H-imidazol-1-yl)methyl)-5-benzyl-2,2-dimethylimidazolidin-4-one 6 in 77% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.10 (s, 3H), 1.22 (s, 3H), 1.90-1.98 (m, 2H), 2.86-2.93 (m, 1H), 3.02-3.11 (m, 2H), 3.30-3.37 (m, 1H), 3.78 (t, $J$ = 5.24 Hz, 1H), 3.81-3.95 (m, 2H), 6.94 (s, 1H),...
Step 5. Alkylation of substrate 6 for the formation of ionic liquid I

(S)-3-((1H-Imidazol-1-yl)methyl)-5-benzyl-2,2-dimethylimidazolidin-4-one 6 (11 mmol, 3.44 g) was dissolved in CH3CN (80 mL), followed by the addition of 1-iodobutane (12 mmol, 2.21 g). The reaction was stirred under refluxing for 23 hours. The progress of the reaction was monitored by 1H NMR analysis. Excess 1-iodobutane (12 mmol, 2.21 g) was added and refluxed for another 23 hrs, and the process was repeated until all the starting material 6 was consumed as indicated by 1H NMR analysis. After reaction, the solvent was evaporated in vacuo and the reaction mixture was purified by silica gel column chromatography using dichloromethane and methanol as eluant to give catalyst I in 80% yield. 1H NMR (400 MHz, CDCl3): 0.91 (t, J = 7.33 Hz, 3H), 1.23 (s, 6H), 1.31-1.36 (m, 2H), 1.83-1.90 (m, 2H), 1.98 -2.05 (m, 1H), 2.14-2.27 (m, 2H), 3.01-3.07 (m, 3H), 3.25-3.32 (m, 1H), 3.75 (t, J = 5.60 Hz, 1H), 4.17-4.26 (m, 3H), 4.37-4.44 (m, 1H), 7.16-7.25 (m, 5H), 7.42 (s, 1H), 7.84 (s, 1H), 9.90 (s, 1H) ppm. 13C NMR (100 MHz, CDCl3): δ 175.3 (C), 136.9 (C), 136.2 (CH), 129.4 (CH x 2), 128.4 (CH x 2), 126.8 (CH), 123.1 (CH), 121.8 (CH), 76.7 (C), 58.9 (CH), 49.9 (CH2), 47.2 (CH2), 36.7 (CH2), 36.3 (CH2), 31.8 (CH2), 30.6 (CH2), 27.9 (CH3), 26.0 (CH3), 19.3 (CH2), 13.3 (CH3) ppm. HRMS (ESI, m/z): [M-I]+, calcd. for C22H33N4O: 369.2649, found: 369.2659.

Step 6. Anion exchange for the preparation of catalysts II and III

A 150 mL round-bottomed flask was charged with catalyst I (5 mmol, 2.48 g), potassium tetrafluoroborate (6 mmol, 0.76 g), water (25 mL), and acetone (25 mL). The reaction mixture was stirred at room temperature for overnight. After reaction, acetone was removed and the aqueous layer was extracted with CH2Cl2 (50 mL x 3). The combined organic layer was washed with water (25 mL x 3), dried with anhydrous MgSO4, filtered and concentrated in vacuo to give catalyst II in quantitative yield. 1H NMR (300 MHz, CDCl3): δ 0.86 (t, J = 7.31 Hz, 3H), 1.18 (s, 6H), 1.24-1.31 (m, 2H), 1.74-1.84 (m, 2H), 1.88-2.03 (m, 3H), 2.88-3.07 (m, 3H), 3.20-3.27 (m, 1H), 3.68 (dd, J = 7.26, 4.08 Hz, 1H), 4.06-4.19 (m, 4H), 7.14-7.20 (m, 5H), 7.38 (s, 1H), 7.58 (s,
A 150 mL round-bottomed flask was charged with catalyst I (5 mmol, 2.48 g), potassium hexafluorophosphate (6 mmol, 1.10 g), water (25 mL), and acetone (25 mL). The reaction mixture was stirred at room temperature for overnight. After reaction, acetone was removed and the aqueous layer was extracted with CH₂Cl₂ (50 mL x 3), the combined organic layer was washed with water (25 mL x 3), dried over anhydrous MgSO₄, filtered and concentrated in vacuo to give catalyst III in quantitative yield. ¹H NMR (300 MHz, CDCl₃): δ 0.94 (t, J = 7.29 Hz, 3H), 1.25 (s, 6H), 1.29-1.41 (m, 2H), 1.80-1.90 (m, 2H), 1.98-2.09 (m, 3H), 3.27-3.38 (m, 1H), 3.76 (dd, J = 7.39, 4.24 Hz, 1H), 4.12-4.16 (m, 4H), 7.20-7.28 (m, 5H), 7.36 (s, 1H), 7.51 (s, 1H), 8.75 (s, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 175.0 (C=O), 137.1 (C), 135.1 (CH), 129.1 (CH x 2), 128.1 (CH x 2), 126.4 (CH), 122.5 (CH), 76.3 (C), 58.7 (CH), 49.4 (CH₂), 47.0 (CH₂), 36.8 (CH₂), 35.9 (CH₂), 31.3 (CH₂), 29.9 (CH₂), 27.3 (CH₂), 25.4 (CH₃), 18.9 (CH₃), 12.9 (CH₃) ppm. HRMS (ESI, m/z): [M-PF₆]+, calcd. for C₂₂H₃₅N₄O: 369.2649, found: 369.2648.

General procedure for the 1,3-dipolar cycloaddition

To a solution of the ionic liquid-supported imidazolidinone catalyst I (0.1 mmol, 0.05 g) in CH₃NO₂ (1.9 mL) and H₂O (0.1 mL) was added HBF₄ (0.1 mmol) and nitron (0.5 mmol). After cooling the solution to -20 °C, α,β-unsaturated aldehyde (2 mmol) was added to the flask with stirring. Additional aldehyde (1 mmol x 3) was added to the reaction mixture at 24 h intervals until the specified reaction time was reached. The resulting solution was evaporated under vacuo and the residue was extracted with diethyl ether (5 mL x 5). The combined organic layer was washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuo and purified by silica gel column chromatography using hexane and ethyl acetate as eluant to afford the desired product. The remaining oil compound in the flask (catalyst I) was dried under vacuo and reused in further reactions by the addition of acid co-catalyst HBF₄ (0.1 mmol), CH₃NO₂ (1.9 mL), and H₂O (0.1 mL).
Spectroscopic data of the 1,3-dipolar cycloaddition products

(4S, 5R)-2-Benzyl-4-formyl-5methyl-3-(4-bromophenyl) isoxazolidine (Table 3, entry 1): $^1$H NMR (400 MHz, CDCl$_3$): (endo isomer) $\delta$ 1.49 (d, $J$ = 6.16 Hz, 3H), 3.03-3.07 (m, 1H), 3.85 (d, $J$ = 14.13 Hz, 1H), 3.96 (d, $J$ = 14.08 Hz, 1H), 4.16 (d, $J$ = 7.48 Hz, 1H), 4.51-4.57 (m, 1H), 7.23-7.31 (m, 7H), 7.46 (d, $J$ = 8.33 Hz, 2H), 9.78 (d, $J$ = 1.16 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): (endo isomer) $\delta$ 198.2 (CH), 137.8 (C), 136.9 (C), 132.1 (CH x 2), 129.2 (CH x 2), 128.5 (CH x 2), 128.3 (CH x 2), 127.3 (CH), 122.0 (C), 73.6 (CH), 71.6 (CH), 70.1 (CH), 59.7 (CH$_2$), 21.0 (CH$_3$) ppm. Enantiomeric ratio was determined by HPLC using Chiracel OD-H column (x 2) after reduction with NaBH$_4$/MeOH (2.5:97.5 i-PrOH/hexane, 2 mL/min flow rate), endo isomers $t_r$ = 22.9 min (major enantiomer) and 31.9 min (minor enantiomer). HRMS (ESI, m/z): [M+H]$^+$, calcd. for C$_{18}$H$_{19}$BrNO$_2$: 360.0599, found: 360.0610.

(4S, 5R)-2-Benzyl-4-formyl-5methyl-3-(4-chlorophenyl) isoxazolidine (Table 3, entry 2): $^1$H NMR (400 MHz, CDCl$_3$): (endo isomer) $\delta$ 1.49 (d, $J$ = 6.16 Hz, 3H), 3.05 (t, $J$ = 5.64 Hz, 1H), 3.84 (d, $J$ = 14.13 Hz, 1H), 3.96 (d, $J$ = 14.00 Hz, 1H), 4.16 (d, $J$ = 7.25 Hz, 1H), 4.51-4.57 (m, 1H), 7.23-7.37 (m, 9H), 9.78 (s, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): (endo isomer) $\delta$ 198.3 (CH), 137.2 (C), 137.0 (C), 129.1 (CH x 2), 128.9 (CH x 2), 128.5 (CH x 2), 128.3 (CH x 2), 127.3 (CH), 73.6 (CH), 71.6 (CH), 70.1 (CH), 59.7 (CH$_3$), 21.0 (CH$_3$) ppm. Enantiomeric ratio was determined by HPLC using Chiracel OD-H column (x 2) after reduction with NaBH$_4$/MeOH (2:98 i-PrOH/hexane, 1 mL/min flow rate); endo isomers $t_r$ = 54.5 min (major enantiomer) and 72.2 min (minor enantiomer). HRMS (ESI, m/z): [M+H]$^+$, calcd. for C$_{18}$H$_{19}$ClNO$_2$: 316.1104, found: 316.1101. Spectroscopic data are identical to the published data.[6]

(4S, 5R)-2-Benzyl-5-methyl-3-phenylisoxazolidine-4-carbaldehyde (Table 3, entry 3): $^1$H NMR (300 MHz, CDCl$_3$): (endo isomer) $\delta$ 1.49 (d, $J$ = 6.21 Hz, 3H), 3.08-3.13 (m, 1H), 3.81 (d, $J$ = 14.31 Hz, 1H), 4.00 (d, $J$ = 14.31 Hz, 1H), 4.15 (d, $J$ = 7.77 Hz, 1H), 4.50-4.58 (m, 1H), 7.20-7.45 (m, 10H), 9.78 (d, $J$ = 2.34 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): (endo isomer) $\delta$ 198.6 (CH), 138.4 (C), 137.3 (C), 128.9 (CH x 2), 128.4 (CH x 2), 128.2 (CH x 2), 128.1 (CH), 127.6 (CH x 2), 127.1 (CH), 73.4 (CH), 71.5 (CH), 71.1 (CH), 59.5 (CH$_2$), 21.0 (CH$_3$) ppm. Enantiomeric ratio was determined by HPLC using Chiracel OD-H column (x 2) after reduction with NaBH$_4$/MeOH (1:99 i-PrOH/hexane, 1 mL/min flow rate); endo isomers $t_r$ = 126.0 min (major enantiomer) and 141.6 min (minor enantiomer). HRMS (ESI, m/z): [M+H]$^+$, calcd. for C$_{19}$H$_{18}$NO$_2$: 313.1282, found: 313.1281.
C_{18}H_{20}NO_{2}: 282.1494, found: 282.1495. Spectroscopic data are identical to the published data.\[6,8]\]

(4S, 5R)-2-Benzyl-4-formyl-5-methyl-3-(4-methylphenyl) isoxazolidine (Table 3, entry 4): \(^1\)H NMR (400 MHz, CDCl\(_3\)): (endo isomer) \(\delta\) 1.49 (d, \(J = 6.16\) Hz, 3H), 2.34 (s, 3H), 3.07-3.11 (m, 1H), 3.78 (d, \(J = 14.40\) Hz, 1H), 3.99 (d, \(J = 14.45\) Hz, 1H), 4.09 (d, \(J = 7.76\) Hz, 1H), 4.50-4.56 (m, 1H), 7.16-7.33 (m, 9H), 9.77 (d, \(J = 1.76\) Hz, 1H) ppm. \(^13\)C NMR (100 MHz, CDCl\(_3\)): (endo isomer) \(\delta\) 198.8 (CH), 138.0 (C), 137.5 (C), 135.1 (C), 129.6 (CH x 2), 128.4 (CH x 2), 128.2 (CH x 2), 127.6 (CH x 2), 127.1 (CH), 73.4 (CH), 71.6 (CH), 71.1 (CH), 59.4 (CH\(_2\)), 21.2 (CH\(_3\)) ppm. Enantiomeric ratio was determined by HPLC using Chiracel OD-H column (x 2) after reduction with NaBH\(_4/\)MeOH (2:98 iPrOH/hexane, 2 mL/min flow rate); endo isomers \(t_r = 21.8\) min (major enantiomer) and 35.0 min (minor enantiomer). HRMS (ESI, m/z): [M+H]\(^+\), calcd. for C_{19}H_{22}NO\(_2\): 296.1651, found: 296.1664. Spectroscopic data are identical to the published data.\[8\]

(4S, 5R)-2-Benzyl-4-formyl-5-methyl-3-(4-methoxyphenyl) isoxazolidine (Table 3, entry 5):

\(^1\)H NMR (400 MHz, CDCl\(_3\)): (endo isomer) \(\delta\) 1.49 (d, \(J = 6.20\) Hz, 3H), 3.06-3.10 (m, 1H), 3.76 (d, \(J = 14.48\) Hz, 1H), 3.80 (s, 3H), 3.99 (d, \(J = 14.44\) Hz, 1H), 4.07 (d, \(J = 7.85\) Hz, 1H), 4.49-4.55 (m, 1H), 6.89 (d, \(J = 8.60\) Hz, 2H), 7.22-7.36 (m, 7H), 9.76 (d, \(J = 2.32\) Hz, 1H) ppm. \(^13\)C NMR (100 MHz, CDCl\(_3\)): (endo isomer) \(\delta\) 198.8 (CH), 159.5 (C), 137.4 (C), 129.9 (C), 128.9 (CH x 2), 128.4 (CH x 2), 128.2 (CH x 2), 127.1 (CH), 114.3 (CH x 2), 73.3 (CH), 71.5 (CH), 70.9 (CH), 59.3 (CH\(_2\)), 55.3 (CH\(_3\)), 21.2 (CH\(_3\)) ppm. Enantiomeric ratio was determined by HPLC using Chiracel OD-H column (x 2) after reduction with NaBH\(_4/\)MeOH (2:98 iPrOH/hexane, 1 mL/min flow rate); endo isomers \(t_r = 79.9\) min (major enantiomer) and 130.2 min (minor enantiomer). HRMS (ESI, m/z): [M+H]\(^+\), calcd. for C_{19}H_{22}NO\(_3\): 312.1600, found: 312.1609. Spectroscopic data are identical to the published data.\[6,8\]

(4S, 5R)-2-Benzyl-4-formyl-5-methyl-3-(2-napthyl) isoxazolidine (Table 3, entry 6):

\(^1\)H NMR (400 MHz, CDCl\(_3\)): (endo isomer) \(\delta\) 1.53 (d, \(J = 6.12\) Hz, 3H), 3.20 (t, \(J = 6.36\) Hz, 1H), 3.87 (d, \(J = 14.32\) Hz, 1H), 4.04 (d, \(J = 14.27\) Hz, 1H), 4.33 (d, \(J = 7.56\) Hz, 1H), 4.56-4.62 (m, 1H), 7.22-7.35 (m, 5H), 7.47-7.49 (m, 2H), 7.58 (d, \(J = 8.53\) Hz, 1H), 7.81-7.86 (m, 4H), 9.82 (s, 1H) ppm. \(^13\)C NMR (100 MHz, CDCl\(_3\)): (endo isomer) \(\delta\) 198.6 (CH), 137.3 (C), 135.8 (C), 133.3 (C), 133.2 (C), 128.9 (CH), 128.5 (CH x 2), 128.2 (CH x 2), 127.9 (CH), 127.7 (CH), 127.2 (CH), 126.9 (CH), 126.4 (CH), 126.3 (CH), 124.9 (CH), 73.6 (CH), 71.5 (CH), 71.3 (CH), 59.6 (CH\(_2\)), 21.1
(S)-2-Benzyl-3-phenylisoxazolidine-4-carbaldehyde (Table 3, entry 7): $^1$H NMR (300 MHz, CDCl$_3$): (endo isomer) $\delta$ 3.37-3.44 (m, 1H), 3.75 (d, $J = 14.11$ Hz, 1H), 3.97 (d, $J = 14.17$ Hz, 1H), 4.04 (d, $J = 7.35$ Hz, 1H), 4.20-4.29 (m, 2H), 7.21-7.48 (m, 10H), 9.76 (d, $J = 2.10$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): (endo isomer) $\delta$ 197.8 (CH), 137.1 (C), 136.2 (C), 128.0 (CH x 2), 127.7 (CH x 2), 127.3 (CH), 127.2 (CH x 2), 126.8 (CH x 2), 126.3 (CH), 69.7 (CH), 64.9 (CH$_2$), 63.3 (CH), 58.7 (CH$_2$) ppm. Enantiomeric ratios were determined by HPLC using Chiracel AD-H column after reduction with NaBH$_4$/MeOH (2.6:97.4 iPrOH/hexane, 2 mL/min flow rate); endo isomers $t_r = 13.3$ min (major enantiomer) and 9.9 min (minor enantiomer). HRMS (ESI, m/z): [M+H]$^+$, calcd. for C$_{19}$H$_{22}$NO$_2$: 296.1651, found: 296.1652.

(4$S$, 5$R$)-2-Benzyl-5-ethyl-3-phenylisoxazolidine-4-carbaldehyde (Table 3, entry 8): $^1$H NMR (300 MHz, CDCl$_3$): (endo isomer) $\delta$ 0.96 (t, $J = 7.38$ Hz, 3H), 1.64-1.78 (m, 1H), 1.92-2.07 (m, 1H), 3.12-3.17 (m, 1H), 3.79 (d, $J = 14.39$ Hz, 1H), 3.99 (d, $J = 14.40$ Hz, 1H), 4.13 (d, $J = 7.80$ Hz, 1H), 4.26 (dd, $J = 5.61$, 12.90 Hz, 1H), 7.20-7.44 (m, 10H), 8.32 (d, $J = 2.34$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): (endo isomer) $\delta$ 198.7 (CH), 138.3 (C), 137.5 (C), 129.0 (CH x 2), 128.4 (CH x 2), 128.2 (CH), 128.2 (CH x 2), 127.6 (CH x 2), 127.1 (CH), 78.8 (CH), 71.1 (CH), 70.1 (CH), 79.4 (CH$_2$), 28.5 (CH$_2$), 10.2 (CH$_3$) ppm. Enantiomeric ratios were determined by HPLC using Chiracel AD-H column after reduction with NaBH$_4$/MeOH (2.6:97.4 iPrOH/hexane, 2 mL/min flow rate); endo isomers $t_r = 13.3$ min (major enantiomer) and 9.9 min (minor enantiomer). HRMS (ESI, m/z): [M+H]$^+$, calcd. for C$_{19}$H$_{22}$NO$_2$: 296.1651, found: 296.1652.
70.4 (CH), 59.4 (CH$_2$), 37.6 (CH$_2$), 19.2 (CH$_2$), 13.9 (CH$_3$) ppm. Enantiomeric ratios were determined by HPLC using Chiracel AD-H column after reduction with NaBH$_4$/MeOH (2:98 iPrOH/hexane, 2 mL/min flow rate); endo isomers t$_r$ = 16.2 min (major enantiomer) and 11.3 min (minor enantiomer). HRMS (ESI, m/z): [M+H]$^+$ calcld. for C$_{20}$H$_{24}$NO$_2$: 310.1807, found: 310.1813. Spectroscopic data are identical to the published data.[8]

References


7. See references 3-5 in the manuscript.

Copies of $^1$H and $^{13}$C NMR spectra of products