

Supplemental Material

Screening of Optically Active Nickel Initiators for Enantioasymmetric Polymerization of γ -Benzyl Glutamate-N-Carboxyanhydride

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Experimental

General Infrared spectra were recorded on a Perkin Elmer 1600 FTIR Spectrophotometer calibrated using polystyrene film. Tandem gel permeation chromatography/light scattering (GPC/LS) was performed on a SSI Accuflow Series III liquid chromatograph pump equipped with a Wyatt DAWN DSP light scattering detector and Wyatt Optilab DSP. Separations were effected by 10^5\AA and 10^3\AA Phenomenex 5μ columns using 0.1M LiBr in DMF eluent at 60 °C. Optical rotations were measured on a Jasco Model P1020 Polarimeter using a 1 mL volume cell (1 dm length). NMR spectra were measured on Bruker AVANCE 200MHz and Varian Gemini 200MHz spectrometers. C, H, N elemental analyses were performed by the Microanalytical Facility of the University of California, Santa Barbara Biology Department. Chemicals were obtained from commercial suppliers and used without purification unless otherwise stated. Hexanes, THF, C_6D_6 , and THF- d_8 were purified by first purging with dry nitrogen, followed by passage through columns of activated alumina.¹

γ -Benzyl-L-glutamate NCA (L-Glu NCA, $[\alpha]_D^{23}$ (THF, $c = 0.025$) = -10.4) and γ -benzyl-D-glutamate NCA (D-Glu NCA, $[\alpha]_D^{23}$ (THF, $c = 0.025$) = +10.3) were prepared according to literature procedures.² Ligands **1** and **2** were purchased from Aldrich Chemical Co. and used without further purification. Synthesis of imine ligands **3,4,6**, and **7** was accomplished by condensation of the corresponding amine and aldehyde components.³ The general procedure for synthesis of pyridinyl-oxazoline ligands **5** and **8-13** involves the reaction of a 2-cyanopyridine and corresponding amino alcohol via a pyridinyl amidate (Scheme 1).⁴ Ligands **5** and **8-13a** were synthesized from a commercially available 2-cyanopyridine. A sample procedure is given below for the synthesis of ligand (**S**)-**8**. Derivatives of 2-cyanopyridine, the building blocks for the synthesis of ligands **13b-13e**, were prepared from the corresponding alkyl pyridine N-oxides.⁵ Results of polymerization of L-Glu NCA with various new nickel initiators are summarized in Table 1.

(4S)-4-Isopropyl-(2-pyridinyl)-2-oxazoline, (S)-8 2-Cyanopyridine (1.4 g, 13 mmol) was added to a solution of sodium methoxide (70 mg, 1.3 mmol) in methanol (12 mL) under nitrogen. The mixture was stirred overnight at room temperature and then acetic acid (13 mmol) was added dropwise. The mixture was stirred for two hours and the methanol was removed under vacuum. Distillation of the residue under reduced pressure afforded the pyridinyl amidate as a colorless oil (1.6 g, 89% yield). IR(neat): 1650 cm^{-1} ($\nu_{\text{C}=\text{NH}}$, vs).

The pyridinyl amidate (0.10 g, 0.80 mmol) was mixed with (**S**)-valinol (0.083 g, 0.80 mmol) in dry methylene chloride (2 mL) under nitrogen. Concentrated HCl (0.01 mL) was added at room temperature. The mixture was then refluxed at 60 °C for 12 hours. CHCl_3 (5 mL) was then added, followed by water (5 mL). The water layer was extracted with CHCl_3 (3 \times 2 mL) and the organic layers were combined and dried with MgSO_4 . After removal of the solvent

under reduced pressure, the light yellow residue was purified by a silica gel flash column with ethyl acetate-petroleum ether (1:1) as eluent ($R_f = 0.5$). (S)-**8** was obtained as white crystals after removal of the solvent under vacuum (110 mg, 72 % yield). IR(CHCl_3): 1644 cm^{-1} ($\nu_{\text{C=N}}$, vs). $^1\text{H NMR}$ (CDCl_3 , see Figure 1 for assignments): δ 8.71 (m, 1H, H_a), 8.07 (m, 1H, H_d), 7.78 (m, 1H, H_c), 7.39 (m, 1H, H_b), 4.52 (m, 1H, H_e), 4.19 (m, 2H, H_e and H_f), 1.91 (m, 1H, H_g), 1.01 (d, 3H, H_h), 0.95 (d, 3H, H_h). Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$: 69.45% C, 7.42% H, 14.73% N; found: 69.03% C, 7.56% H, 14.65% N. $[\alpha]_D^{23}$ (THF, $c = 0.043$) = -78.

4,4-Dimethyl-(2-pyridinyl)-2-oxazoline, 5 The same procedure used to synthesize (S)-**8** was followed by using 2-amino-2-methyl-1-propanol and 2-cyanopyridine as starting materials (82% yield). IR(CHCl_3): 1644 cm^{-1} ($\nu_{\text{C=N}}$, vs). $^1\text{H NMR}$ (CDCl_3 , see Figure 1 for assignments): δ 8.63 (d, 1H, H_a), 7.94 (d, 1H, H_d), 7.69 (t, 1H, H_c), 7.31 (t, 1H, H_b), 4.13 (s, H_e), 1.34 (s, 6H, H_f). Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}$: 68.16% C, 6.86% H, 15.90% N; found: 68.21% C, 6.84% H, 15.85% N.

(4R)-4-Isopropyl-(2-pyridinyl)-2-oxazoline, (R)-8 The same procedure used to synthesize (S)-**8** was followed by using (R)-valinol and 2-cyanopyridine as starting materials (66% yield). IR(CHCl_3): 1644 cm^{-1} ($\nu_{\text{C=N}}$, vs). $^1\text{H NMR}$ (CDCl_3 , see Figure 1 for assignments): δ 8.71 (m, 1H, H_a), 8.07 (m, 1H, H_d), 7.78 (m, 1H, H_c), 7.39 (m, 1H, H_b), 4.52 (m, 1H, H_e), 4.19 (m, 2H, H_e and H_f), 1.91 (m, 1H, H_g), 1.01 (d, 3H, H_h), 0.95 (d, 3H, H_h). $[\alpha]_D^{23}$ (THF, $c = 0.060$) = +78.

(4S, 5R)-4,5-Indanyl-(2-pyridinyl)-2-oxazoline, 9 The same procedure used to synthesize (S)-**8** was followed by using (1S, 2R)-*cis*-1-amino-2-indanol and 2-cyanopyridine as starting materials (69% yield). IR(CHCl_3): 1634 cm^{-1} ($\nu_{\text{C=N}}$, vs). $^1\text{H NMR}$ (CDCl_3 , see Figure 1 for assignments): δ 8.69 (m, 1H, H_a), 8.04 (m, 1H, H_d), 7.70 (m, 1H, H_c), 7.58 (m, 1H, H_b),

7.30 (m, 4H, H_{h-k}), 5.81 (d, 1H, H_f), 5.59 (m, 1H, H_e), 3.50 (d, 2H, H_g). Anal. Calcd. for C₁₅H₁₂N₂O: 76.25%C, 5.12%H, 11.86%N; found: 75.80%C, 5.48%H, 11.99%N. $[\alpha]_D^{23}$ (CHCl₃, c = 0.039) = -157.

(4S, 5R)-4,5-Diphenyl-(2-pyridinyl)-2-oxazoline, 10 The same procedure used to synthesize (S)-8 was followed by using (1R, 2S)-2-amino-1, 2-diphenylethanol and 2-cyanopyridine as starting materials (50% yield). IR(CHCl₃): 1644 cm⁻¹ (νC=N, vs). ¹H NMR (CDCl₃, see Figure 1 for assignments): δ 8.61 (m, 1H, H_a), 8.07 (m, 1H, H_d), 7.62 (m, 1H, H_c), 7.22 (m, 1H, H_b), 6.82 (m, 10H, H_g and H_h), 5.94 (d, 1H, H_f), 5.66 (d, 1H, H_e). Anal. Calcd. for C₂₀H₁₆N₂O: 79.98%C, 5.37%H, 9.32%N; found: 79.90%C, 5.38%H, 9.33%N. $[\alpha]_D^{23}$ (CHCl₃, c = 0.020) = -159.

(4S, 5S)-4-Hydroxymethyl-5-phenyl-(2-pyridinyl)-2-oxazoline, 11 The same procedure used to synthesize (S)-8 was followed by using (1S, 2S)-2-amino-1-phenyl-1, 3-propanediol and 2-cyanopyridine as starting materials (78% yield). IR(CHCl₃): 1643 cm⁻¹ (νC=N, vs). ¹H NMR (CDCl₃, see Figure 1 for assignments): δ 8.67 (d, 1H, H_a), 7.96 (d, 1H, H_d), 7.73 (m, 1H, H_c), 7.38 (m, 6H, H_b and H_g), 5.71 (d, 1H, H_i), 4.35 (dd, 1H, H_e), 4.19 (m, 1H, H_f), 3.83 (dd, 2H, H_h). Anal. Calcd. for C₁₅H₁₄N₂O₂: 70.85%C, 5.55%H, 11.02%N; found: 69.65%C, 5.43%H, 10.63%N. $[\alpha]_D^{23}$ (CHCl₃, c = 0.025) = +21.

(4S)-4-Phenyl-(2-pyridinyl)-2-oxazoline, 12 The same procedure used to synthesize (S)-8 was followed by using (S)-2-phenyl glycinol and 2-cyanopyridine as starting materials (88% yield). IR(CHCl₃): 1646 cm⁻¹ (νC=N, vs). ¹H NMR (CDCl₃, see Figure 1 for assignments): δ 8.69 (d, 1H, H_a), 8.12 (d, 1H, H_d), 7.75 (m, 1H, H_c), 7.38 (m, 1H, H_b), 7.35 (s, 5H, H_g), 5.42 (dd (ABX), 1H, H_e), 4.86 (dd (ABX), 1H, H_f), 4.34 (dd (ABX), 1H, H_e). Anal. Calcd. for

$C_{14}H_{12}N_2O$: 74.98%C, 5.39%H, 12.49%N; found: 74.60%C, 5.49%H, 12.67%N. $[\alpha]_D^{24}$ (THF, $c = 0.025$) = -85.

(4S)-4-*tert*-Butyl-(2-pyridinyl)-2-oxazoline, 13a The same procedure used to synthesize (S)-8 was followed by using (S)-*tert*-leucinol and 2-cyanopyridine as starting materials (64% yield). IR($CHCl_3$): 1650 cm^{-1} ($\nu_{C=N}$, vs). 1H NMR ($CDCl_3$, see Figure 1 for assignments): δ 8.72 (m, 1H, H_a), 8.10 (m, 1H, H_d), 7.79 (m, 1H, H_c), 7.39 (m, 1H, H_b), 4.47 (dd (ABX), 1H, H_e), 4.33 (dd (ABX), 1H, H_f), 4.13 (dd (ABX), 1H, H_e), 0.98 (s, 9H, H_g). ^{13}C NMR ($CDCl_3$): δ 163.5, 150.8, 148.1, 137.6, 126.5, 125.1, 77.6, 70.4, 35.0, 27.1. Anal. Calcd. for $C_{12}H_{16}N_2O$: 70.56%C, 7.90%H, 13.71%N; found: 71.25%C, 7.86%H, 13.48%N. $[\alpha]_D^{23}$ (THF, $c = 0.023$) = -70.

(4S)-4-*tert*-Butyl-(2-(6-methyl)-pyridinyl)-2-oxazoline, 13b The same procedure used to synthesize (S)-8 was followed by using (S)-*tert*-leucinol and 2-cyano-6-methylpyridine as starting materials (66% yield). IR($CHCl_3$): 1650 cm^{-1} ($\nu_{C=N}$, vs). 1H NMR ($CDCl_3$, see Figure 1 for assignments): δ 7.95 (d, 1H, H_d), 7.65 (dd, 1H, H_c), 7.27 (d, 1H, H_b), 4.47 (dd (ABX), 1H, H_e), 4.35 (dd (ABX), 1H, H_f), 4.11 (dd (ABX), 1H, H_e), 2.64 (s, 3H, H_a), 0.97 (s, 9H, H_g). Anal. Calcd. for $C_{13}H_{18}N_2O$: 71.53%C, 8.31%H, 12.83%N; found: 70.85%C, 8.56%H, 12.63%N. $[\alpha]_D^{23}$ ($CHCl_3$, $c = 0.036$) = -97.

(4S)-4-*tert*-Butyl-(2-(6-ethyl)-pyridinyl)-2-oxazoline, 13c The same procedure used to synthesize (S)-8 was followed by using (S)-*tert*-leucinol and 2-cyano-6-ethylpyridine as starting materials (79% yield). IR($CHCl_3$): 1650 cm^{-1} ($\nu_{C=N}$, vs). 1H NMR ($CDCl_3$, see Figure 1 for assignments): δ 7.90 (d, 1H, H_e), 7.61 (dd, 1H, H_d), 7.21 (d, 1H, H_c), 4.40 (dd (ABX), 1H, H_f), 4.26 (dd (ABX), 1H, H_g), 4.04 (dd (ABX), 1H, H_f), 2.87 (q, 2H, H_b), 1.23 (t, 3H, H_a), 0.91 (s,

9H, H_h). Anal. Calcd. for C₁₄H₂₀N₂O: 72.38%C, 8.68%H, 12.06%N; found: 71.76%C, 8.93%H, 12.28%N.

(4S)-4-*tert*-Butyl-(2-(6-phenyl)-pyridinyl)-2-oxazoline, 13d The same procedure used to synthesize (S)-8 was followed by using (S)-*tert*-leucinol and 2-cyano-6-phenylpyridine as starting materials (85% yield). IR(CHCl₃): 1650 cm⁻¹ (νC=N, vs). ¹H NMR (CDCl₃, see Figure 1 for assignments): δ 8.07 (m, 3H, H_b, H_c and H_d), 7.80 (m, 2H, H_a), 7.43 (m, 3H, H_a), 4.48 (dd (ABX), 1H, H_e), 4.34 (dd (ABX), 1H, H_f), 4.13 (dd (ABX), 1H, H_e), 0.99 (s, 9H, H_g). Anal. Calcd. for C₁₈H₂₀N₂O: 77.11%C, 7.19%H, 9.99%N; found: 77.29%C, 7.29%H, 10.00%N. [α]_D²³ (CHCl₃, c = 0.008) = -100.

(4S)-4-*tert*-Butyl-(2-(3-methyl)-pyridinyl)-2-oxazoline, 13e The same procedure used to synthesize (S)-8 was followed by using (S)-*tert*-leucinol and 2-cyano-3-methylpyridine⁶ as starting materials (67% yield). IR(CHCl₃): 1650 cm⁻¹ (νC=N, vs). ¹H NMR (CDCl₃, see Figure 1 for assignments): δ 8.57 (d, 1H, H_a), 7.57 (d, 1H, H_c), 7.26 (m, 1H, H_b), 4.40 (dd (ABX), 1H, H_e), 4.19 (dd (ABX), 2H, H_e and H_f), 2.63 (s, 3H, H_d), 0.98 (s, 9H, H_g). Anal. Calcd. for C₁₃H₁₈N₂O: 71.53%C, 8.31%H, 12.83%N; found: 71.80%C, 8.45%H, 12.57%N. [α]_D²³ (CHCl₃, c = 0.018) = -77.

Sample procedure for kinetic studies (S)-8 was mixed in a equimolar ratio with Ni(COD)₂ in THF in a dry box. The resulting blue solution of (S)-8Ni(COD) (0.019 M) was aged for 8-12 h at 23 °C. An aliquot of initiator solution (0.25 ml) was added to a well stirred solution of L-Glu NCA (25 mg, 0.10 mmol) in THF (1.25 ml). The resulting red solution was stirred for 2 min, and then divided into 6 equal portions (0.25 mL) and each injected into an ampule. The ampules were sealed with grease and then placed in a thermostated bath. The intensity of the NCA infrared stretching absorption at 1790 cm⁻¹ was measured at various time

intervals by injecting an aliquot of polymerization solution into a Wilmad 0.1 mm NaCl cell. The polymerization rate constant was obtained by plotting the log of the NCA concentration versus time and fitting the data using standard rate expressions:

Polymerization of Glu-NCA with 5Ni(COD) In the dry box, Glu NCA (50 mg, 0.2 mmol) was dissolved in THF (0.5 mL) and placed in a 25 mL reaction tube which could be sealed with a Teflon stopcock. An aliquot of 5Ni(COD) (100 μ L of a 0.019 M solution in THF) was then added *via* syringe to the flask. A stirbar was added and the flask was sealed, removed from the dry box, and stirred at room temperature for 24 h. Polymer was isolated by addition of the reaction mixture to methanol containing HCl (1 mM) causing precipitation of the polymer. The polymer was then dissolved in THF and reprecipitated by addition to methanol. The polymer was dried *in vacuo* to give a white solid, PBLG (41 mg, 100% yield). ^{13}C { ^1H } NMR, ^1H NMR, optical rotation, and FTIR spectra of this material were identical to data found for authentic samples of PBLG.⁷ GPC of the polymer in 0.1 M LiBr in DMF at 60 $^\circ\text{C}$: $M_n = 80,100$; $M_w/M_n = 1.05$.

Polymerization of Racemic-Glu NCA with 13aNi(COD) and Measurement of Specific Rotation of the Resulting Polypeptides. In the dry box, racemic-Glu NCA (100 mg, 0.40 mmol) was dissolved in THF (1 mL) and placed in a 25 mL reaction tube which could be sealed with a Teflon stopcock. An aliquot of 13aNi(COD) (200 μ L of a 0.019 M solution in THF) was then added *via* syringe to the flask. A stirbar was added and the flask was sealed, removed from the dry box, and stirred at 35 $^\circ\text{C}$ for a prescribed time period. The polymerization time required to yield a desired monomer conversion was determined by kinetic analysis of the racemic polymerization. Polymer was isolated by addition of the reaction mixture to methanol containing HCl (1 mM) causing precipitation of the polymer. The polymer was then dissolved in

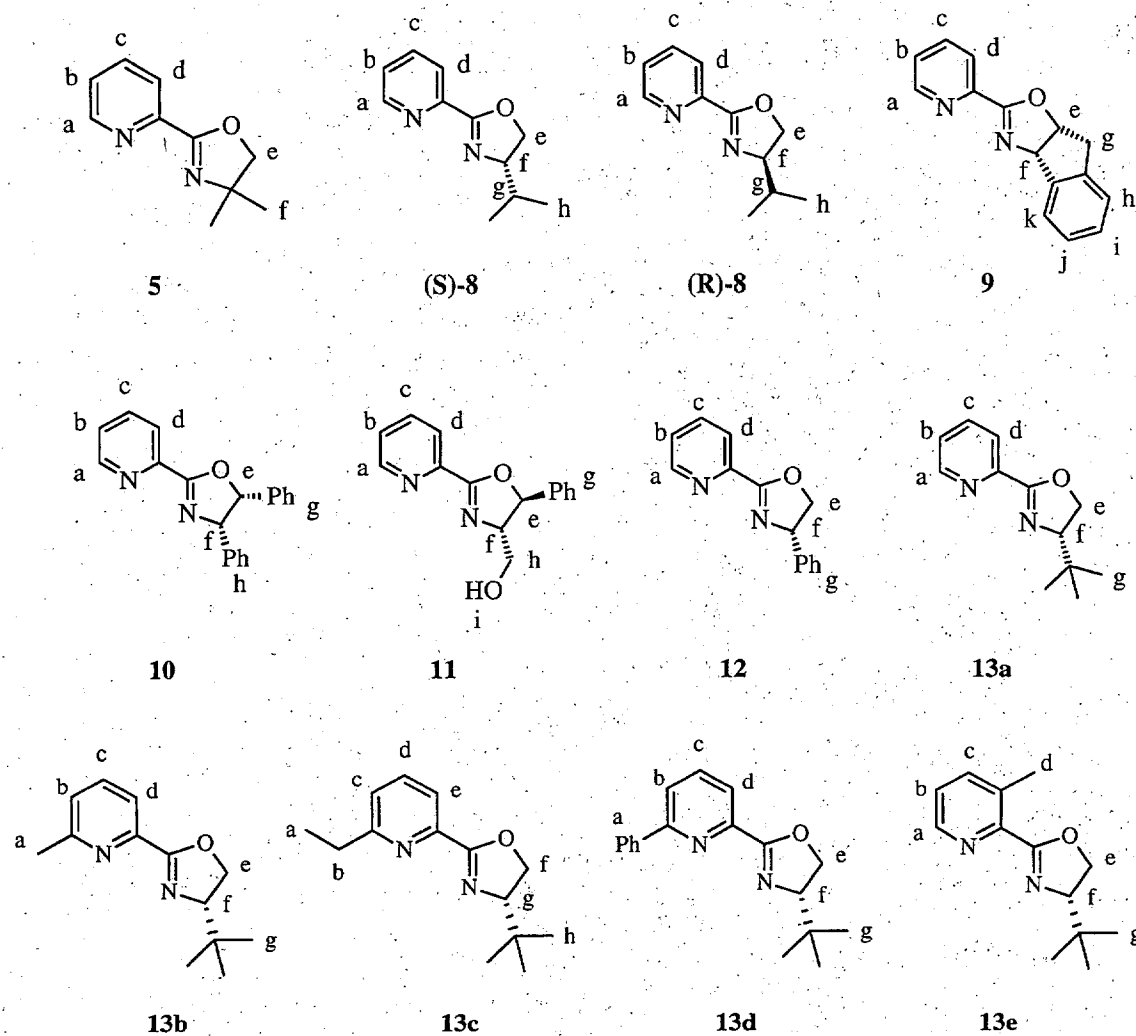
THF and reprecipitated by addition to methanol. The reprecipitation was repeated twice for thorough removal of any residual chiral ligand **13a** from the polymer. The polymer was dried *in vacuo* at room temperature for 10 hours and then weighed to determine the yield and percent conversion. A sample of polymer (usually 5-10 mg) was dissolved in 2 mL Dichloroacetic acid (DCA). The optical rotation of the resulting polymer solution was then measured at 25 °C. Ten measurements were taken for each sample where the standard deviation was typically within $\pm 0.001^\circ$. The specific rotation was then calculated from the average of the observed optical rotations. The specific rotations of pure PBLG and PBDG (-16.8 and $+16.8$ respectively) were also measured under the same conditions. The percent enantiomeric excess (%ee) of antipode in a stereocopolymer was calculated by dividing the specific rotation of the copolymer, multiplied by 100, by the specific rotation of either PBLG or PBDG.

References

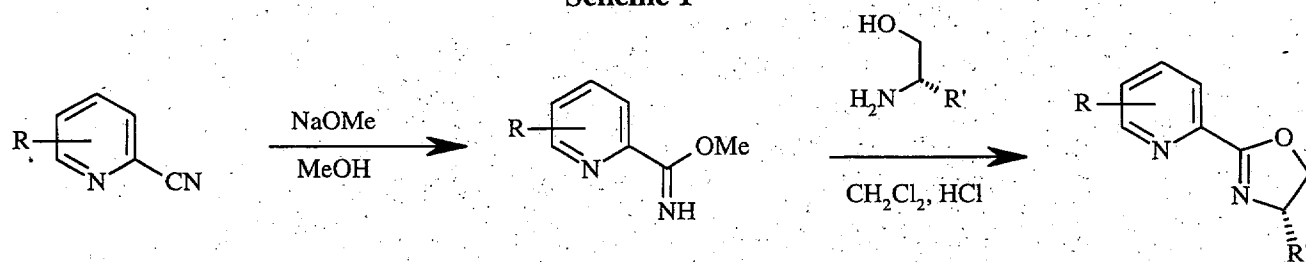
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Figure 1



Scheme 1



S10

[M]/[I]	Initiator	Yield (%)	Expected Mn (kDa)	Observed Mn (kDa)	Mw/Mn
50	5Ni(COD)	100	11	14.9	1.15
100	5Ni(COD)	100	21.9	32.6	1.11
50	13aNi(COD)	91	10	10.4	1.28
100	13aNi(COD)	91	19.9	19.7	1.28

Table 1 Polymerization of L-Glu NCA using nickel initiators. All polymerizations were run in DMF at 20 °C. [M] = initial monomer concentration; [I] = initiator concentration.