ELECTRONIC SUPPLEMENTARY INFORMATION

A copper-templated, bifunctional organocatalyst: a strongly cooperative dynamic system for the aldol reaction

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1. Experimental section

All the reagents and solvents were purchased from commercial suppliers and used without further purification. Anhydrous solvents were obtained from a Solvent Purification System. TLC was performed on silica gel 60 F254 Aluminium sheets. Flash chromatography was performed using silica gel P60 (200-500 mesh). HPLC analyses were performed using a modular equipment with autosampler and UV-Vis detector. NMR spectra were recorded on an automated instrument (400 MHz for $^1$H and 101 MHz for $^{13}$C). The chemical shifts are reported in ppm relative to tetramethylsilane (TMS), and coupling constants ($J$) are reported in Hertz (Hz). Proton signal multiplicities are given as a s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad) or a combination of them. High resolution Mass Spectrometry analyses were performed using a MALDI TOF/TOF mass spectrometer. Optical rotations were measured at 25 °C in a 1 dl cell using the sodium D line as wavelength. EPR spectra were recorded in a quartz tube using THF/water as solvent. UV-Vis spectra were recorded in THF/water using a quartz cell. Infrared spectra were recorded neat on an FTIR spectrometer equipped with ATR.

Synthesis of pyridine-prolinamide ligands P2, P3 and P4.

General procedure for the synthesis of Z-protected-P2, -P3 and –P4.

To a solution of N-carbobenzyloxy-L-proline (1 g, 4 mmol) and triethylamine (557 µL, 4 mmol) in dry THF (15 mL) under nitrogen atmosphere at 0°C was added ethyl chloroformate (382 µL, 4 mmol) dropwise and the reaction mixture was stirred for 30 min at 0 °C. Then, the corresponding aminopyridine (2-, 3- or 4-aminopyridine respectively, 376 mg, 4 mmol) was added and the resulting reaction was stirred at 0°C for 1 h and at 70°C for 24 h. After cooling down to room temperature, the mixture was diluted with EtOAc (150 mL), filtered and the solvent was evaporated. The crude was purified by flash chromatography on silica gel using Hexane/ethyl acetate to give Z-P.

Benzyl (S)-2-(pyridin-2-ylcarbamoyl) pyrrolidine-1-carboxylate (Z-P2): Yield: 83% (colorless wax). FTIR (ATR): 2955, 2881, 1695, 1576, 1531, 1433, 1353, 1298, 1177, 1117, 1088 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ (ppm) 9.52 (bs, 1H), 8.25 (m, 2H), 7.72 (m, 1H), 7.40 (m, 3H), 7.08 (m, 3H), 5.15 (s, 2H), 4.45 (m, 1H), 3.57 (m, 2H), 2.21 (m, 2H), 1.95 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (ppm) 171.0, 152.1, 151.3, 147.1, 146.6, 138.9, 136.3, 128.5, 128.1, 128.0, 119.8, 118.3, 114.8, 67.5, 61.6, 47.2, 29.3, 24.6. MS (ESI-TOF): 326.1471 (M+H)$^+$ (calcd. mass for C$_{18}$H$_{20}$N$_3$O$_3$ (M+H)$^+$: 326.1506), 348.1308 (M+Na)$^+$ (calcd. mass for C$_{18}$H$_{19}$N$_3$NaO$_3$ (M+Na)$^+$: 348.1326), 673.2852 (2M+Na)$^+$ (calcd. mass for C$_{36}$H$_{38}$N$_6$NaO$_6$ (2M+Na)$^+$ 673.2752).

Benzyl (S)-2-(pyridin-3-ylcarbamoyl) pyrrolidine-1-carboxylate (Z-P3): Yield: 70% (colorless wax). FTIR (ATR): 2955, 2881, 1695, 1576, 1531, 1433, 1353, 1298, 1177, 1117, 1108 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ (ppm) 9.42 (bs, 1H), 8.54 (bs, 1H), 8.01 (bs, 1H), 7.45 (b, 4H), 7.20 (dd, J=8 Hz, J=4 Hz, 1H), 5.20 (bs, 2H), 4.50 (bs, 1H), 3.48 (m, 2H), 2.52 (m, 1H), 1.94 (m, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (ppm) 170.6 (C), 156.7 (C), 143.9 (CH), 139.9 (CH), 136.3 (C), 135.8 (C), 128.7 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 124.1 (CH), 67.8 (CH$_2$), 60.9 (CH), 47.3 (CH$_2$), 28.2 (CH$_3$), 24.7 (CH$_3$). MS (ESI-TOF): 326.1471
(M+H)⁺ (calcd. mass for C₁₈H₂₀N₃O₃ (M+H)⁺: 326.1506), 651.2960 (2M+H)⁺ (calcd. mass for C₃₆H₃₉N₆O₆ (2M+H)⁺: 651.2932).

Benzyl (S)-2-(pyridin-4-ylcarbamoyl) pyrrolidine-1-carboxylate (Z-P4):¹⁴ Yield: 64% (colorless wax). FTIR (ATR): 3277, 2970, 2882, 1673, 1591, 1514, 1448, 1413, 1353, 1326, 1290, 1171, 1119, 1087 cm⁻¹.¹H NMR (400 MHz, CDCl₃, rotamers) δ (ppm) 9.68 (bs, 1H), 8.39 (d, J = 5.5 Hz, 2H), 7.35 (m, 6H), 5.21 (bs, 2H), 4.50 (bs, 1H), 3.46 (m, 2H), 2.46 (bs, 1H), 1.97 (m, 3H).¹³C NMR (101 MHz, CDCl₃) δ (ppm) 170.3, 150.0, 145.4, 136.0, 128.6, 128.3, 127.9, 113.7, 67.9, 61.1, 47.2, 27.2, 24.6. MS (ESI-TOF): 326.1465 (M+H)+ (calcd. mass for C₁₈H₂₀N₃O₃ (M+H)⁺: 326.1506), 651.2932 (2M+H)⁺ (calcd. mass for C₃₆H₃₉N₆O₆ (2M+H)⁺: 651.2932).

General procedure for the synthesis of P2, P3 and P4 ligands:

Compound Z-P2, -P3, or –P4 (839 mg, 2.58 mmol) was dissolved in MeOH (20 mL) under nitrogen. After addition of 10 % Pd/C catalyst (83.9 mg), the reaction mixture was stirred at rt for 24 h under hydrogen atmosphere (1.5 atm). After this time, the catalyst was removed by filtration through Celite®, and the solvent was evaporated. If necessary, the crude product was purified by flash chromatography using AcOEt/MeOH.

(S)-N-(pyridin-2-yl)pyrrolidine-2-carboxamide (P2):¹⁴ Yield: 54% (colorless oil). FTIR (ATR): 3261, 3060, 2965, 2870, 1682, 1589, 1574, 1501, 1432, 1297, 1147, 1094 cm⁻¹.¹H NMR (400 MHz, CDCl₃) δ (ppm) 10.22 (bs, 1H), 8.24 (m, 2H), 7.68 (m, 1H), 7.01 (m, 1H), 3.93 (dd, J = 9.3, 5.2 Hz, 1H), 3.06 (m, 2H), 2.22 (m, 1H), 2.10 (bs, 1H), 2.03 (m, 1H), 1.77 (m, 2H).¹³C NMR (101 MHz, CDCl₃) δ (ppm) 174.4, 151.1, 147.9, 138.2, 119.5, 113.5, 60.9, 47.3, 30.8, 26.2. MS (ESI-TOF): 192.1112 (M+H)⁺ (calcd. mass for C₁₀H₁₄N₃O (M+H)⁺: 192.1139), 214.0954 (M+Na)⁺ (calcd. mass for C₁₀H₁₃N₃NaO (M+Na)⁺: 214.1059). [α]²⁰D = -56.5 (c = 1.0, CH₃OH).

(S)-N-(pyridin-3-yl)pyrrolidine-2-carboxamide (P3):¹⁴ Yield: 90% (colorless oil). FTIR (ATR): 3261, 3060, 2969, 2870, 1674, 1582, 1510, 1480, 1419, 1327, 1288, 1188, 1100 cm⁻¹.¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.85 (s, 1H), 8.58 (d, J = 2.6, 1H), 8.31 (ddd, J = 8.3, 2.6, 1.5 Hz, 1H), 7.26 (m, 1H), 3.86 (dd, J = 9.3, 5.2 Hz, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 2.20 (bs, 1H), 2.19 (m, 1H), 2.12 (m, 2H), 2.00 (m, 1H), 1.73 (m, 2H).¹³C NMR (101 MHz, CDCl₃) δ (ppm) 174.4, 151.1, 147.9, 138.2, 119.5, 113.5, 60.9, 47.3, 30.8, 26.2. MS (ESI-TOF): 192.1108 (M+H)⁺ (calcd. mass for C₁₀H₁₄N₃O (M+H)⁺: 192.1139), 214.0924 (M+Na)⁺ (calcd. mass for C₁₀H₁₃N₃NaO (M+Na)⁺: 214.1059), 405.2014 (2M+Na)⁺ (calcd. mass for C₂₀H₂₆N₆NaO₂ (2M+Na)⁺: 405.2118). [α]²⁰D = -60.2 (c = 1.0, CH₃OH).

(S)-N-(pyridin-4-yl)pyrrolidine-2-carboxamide (P4):¹⁴ Yield: quant. (white solid). FTIR (ATR): 3261, 3060, 2965, 2870, 1682, 1589, 1574, 1501, 1432, 1297, 1147, 1094 cm⁻¹.¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.92 (bs, 1H), 8.46 (m, 2H), 7.50 (m, 2H), 3.83 (dd, J = 9.3, 5.2 Hz, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 2.20 (bs, 1H), 2.19 (m, 1H), 2.12 (m, 2H), 2.00 (m, 1H), 1.73 (m, 2H).¹³C NMR (101 MHz, CDCl₃) δ (ppm) 174.6, 150.8, 144.6, 113.4, 61.2, 47.5, 30.8, 26.5. MS (ESI-TOF): 192.1120 (M+H)⁺ (calcd. mass for C₁₀H₁₄N₃O (M+H)⁺: 192.1139). [α]²⁰D = -43.8 (c = 1.0, CH₃OH).
Synthesis of pyridine-thiourea ligand 1-(3,5-bis(trifluoromethyl)phenyl)-3-(pyridin-3-yl)thiourea (T3). \(^1\)

To a solution of 3-aminopyridine (1 g, 10.6 mmol) in dry THF (19 mL) under nitrogen atmosphere at 0°C, 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.94 mL, 10.6 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was evaporated and the crude was purified by flash chromatography on silica gel using hexane/ethyl acetate mixtures to give T3. Yield: 90% (white solid). IR (ATR) 3325, 3097, 3028, 1525, 1474, 1390, 1311, 1274, 1239, 1165, 1124 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) (ppm) 8.66 (dd, \(J = 2.6, 0.7\) Hz, 1H), 8.37 (dd, \(J = 4.9, 1.5\) Hz, 1H), 8.24 (bs, 2H), 8.09 (ddd, \(J = 8.3, 2.6, 1.5\) Hz, 1H), 7.72 (bs, 1H), 7.47 (dd, \(J = 8.3, 4.9, 1.9\) Hz). \(^13\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) (ppm) 182.9, 146.6, 146.3, 142.8, 137.8, 134.1, 132.7 (q, \(^1J_{CF} = 33\) Hz), 125.0, 124.8 (bq), 124.7 (q, \(^1J_{CF} = 273\) Hz), 118.6 (m). \(^19\)F NMR (376 MHz, CD\(_3\)OD) \(\delta\) (ppm) -64.5. MS (ESI-TOF): 366.0468 (M+H)\(^{+}\) (calcd. mass for C\(_{14}\)H\(_{10}\)F\(_6\)N\(_3\)S (M+H)\(^{+}\): 366.0500).

Synthesis of thiourea ligand 1-(3,5-bis(trifluoromethyl)phenyl)-3-phenylthiourea (T). \(^2\)

To a solution of aniline (485 µL, 5.3 mmol) in dry THF (9.5 mL) under nitrogen atmosphere, 3,5-Bis(trifluoromethyl)phenyl Isothiocyanate (1 mL, 5.3 mmol) was added at 0°C. The mixture was stirred overnight at room temperature. Then, the solvent was evaporated. If necessary, the crude product was purified by flash chromatography using hexane/ethyl acetate to give T. Yield: 100% (white solid). IR (ATR) 3217, 1537, 14974, 1383, 1351, 1276, 1175, 1131, 1108 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.45 (bs, 1H), 7.97 (s, 2H), 7.77 (bs, 1H), 7.68 (s, 1H), 7.51 (m, 1H), 7.40 (m, 2H), 7.30 (m, 2H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) (ppm) 179.9, 139.7, 135.6, 132.2 (q, \(^2J_{CF} = 34\) Hz), 130.7, 128.5, 125.7, 124.7 (bq), 123.3 (q, \(^1J_{CF} = 273\) Hz), 119.6 (m). \(^19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) (ppm) -63. MS (ESI-TOF): 365.1 (M+H)\(^{+}\); calculated for C\(_{15}\)H\(_{11}\)F\(_6\)N\(_2\)S: 365.1 (M+H)\(^{+}\).

General procedure for the asymmetric aldol reaction.

A mixture of CuSO\(_4\)·5H\(_2\)O (0.92 mg, 3.7·10\(^{-3}\) mmol, 1 mol %), P3 (14 mg, 0.074 mmol, 20 mol %) and T3 (27 mg, 0.074 mmol, 20 mol %,) was stirred in dry THF (528 µL) and H\(_2\)O (13 µL, 1.1 mmol with respect to aldehyde) at room temperature for 1 h. Then, the aldehyde (0.37 mmol) and ketone (3.7 mmol) were added. The resulting mixture was stirred at rt for 15-24 h. The reaction was quenched with water and the organic phase was extracted with diethyl ether(x3). The combined organic layers were dried over anhydrous MgSO\(_4\), the solvent was evaporated and the crude product was purified by flash chromatography eluting with hexane/ethyl acetate mixtures of increasing polarity.

\(^1\)H NMR on the crude samples was performed to determine conversion and diastereoselectivity. The enantiomeric excess was determined by HPLC on chiral stationary phase (See below for details).
2. **$^1$H NMR and HPLC data of aldol products:**

$^1$H NMR (400 MHz, CDCl$_3$)\textsuperscript{1,6,7} 

\[\delta \text{ (ppm) 7.52 (m, 1H), 7.34 – 7.25 (m, 2H), 7.22 – 7.14 (m, 1H), 5.33 (dd, } J = 8.2, 3.8 \text{ Hz, 1H), 4.00 (s, 1H), 2.66 (m, 1H), 2.44 (m, 1H), 2.37 – 2.26 (m, 1H), 2.06 (m, 1H), 1.79 (m, 1H), 1.74 – 1.60 (m, 2H), 1.59 – 1.48 (m, 2H).}\textsuperscript{1,6,7}

HPLC (ID column, 1 mL/min, 3% iso-propanol, 209 nm)
$^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.30 (m, 2H), 7.23 (m, 2H), 4.74 (dd, J = 8.7, 2.5 Hz, 1H), 3.97 (d, J = 2.8 Hz, 1H), 2.59 – 2.41 (m, 2H), 2.33 (m, 1H), 2.07 (m, 1H), 1.77 (m, 1H), 1.71 – 1.44 (m, 3H), 1.35 – 1.15 (m, 1H).$^{1,6,7}$

HPLC (IC column, 1 mL/min, 10% iso-propanol, 209 nm)
$^1$H NMR (400 MHz, CDCl$_3$)$^1$-$^8$

$^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.49 (m, 1H), 7.26 (m, 2H), 7.17 (m, 1H), 4.97 (dd, $J = 8.7, 2.5$ Hz, 1H), 4.22 (d, $J = 2.8$ Hz, 1H), 2.77 (m, 1H), 2.67 (m, 1H), 2.59 – 2.47 (m, 1H), 2.28 (m, 1H), 1.99 (m, 1H), 1.93 – 1.67 (m, 3H), 1.49 (m, 1H)$^1$-$^8$

HPLC (ID column, 1 mL/min, 3% iso-propanol, 209 nm)
$^1$H NMR (400 MHz, CDCl$_3$)$^{1,7,9,10}$

$^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.60 (d, $J = 8.1$ Hz, 2H), 7.44 (d, $J = 8.1$ Hz, 2H), 4.84 (dd, $J = 8.6$, 2.7 Hz, 1H), 4.03 (m, 1H), 2.59 (m, 1H), 2.49 (m, 1H), 2.36 (m, 1H), 2.10 (m, 1H), 1.81 (m, 1H), 1.74 – 1.44 (m, 3H), 1.39 – 1.22 (m, 1H). $^{1,7,9,10}$

HPLC (ID column, 1 mL/min, 3% iso-propanol, 209 nm)
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.21 (d, $J = 8.8$ Hz, 2H), 7.49 (m, 2H), 4.90 (dd, $J = 8.4$, 3.1 Hz, 1H), 4.06 (d, $J = 3.2$ Hz, 1H), 2.59 (m, 1H), 2.53 – 2.45 (m, 1H), 2.37 (m, 1H), 2.12 (m, 1H), 1.83 (m, 1H), 1.67 (m, 1H), 1.63 – 1.56 (m, 2H), 1.38 (m, 1H). $^{1,7,9,11}$

HPLC (OD column, 1 mL/min, 5% iso-propanol, 209 nm)

$[\alpha]_D = +9.1$ (c=0.96, CHCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$; syn diastereomer) δ (ppm) 8.19 (m, 2H), 7.48 (m, 2H), 5.40 (m, 1H), 2.58 (m, 1H), 2.51 – 2.31 (m, 2H), 2.19 (m, 1H), 2.07 – 1.87 (m, 2H), 1.80 – 1.63 (m, 2H).\(^{1,7,9,11}\)

$^1$H NMR (400 MHz, CDCl$_3$; anti diastereomer) δ (ppm) 8.19 (m, 2H), 7.48 (m, 2H), 4.82 (m, 1H), 4.72 (s, 1H), 2.51 – 2.31 (m, 2H), 2.19 (m, 1H), 2.07 – 1.87 (m, 2H), 1.80 – 1.63 (m, 2H).\(^{1,7,9,11}\)

HPLC (IC column, 1 mL/min, 10% iso-propanol, 209 nm)
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.17 (d, $J = 8.8$ Hz, 2H), 7.52 (d, $J = 8.5$ Hz, 2H), 5.24 (dd, $J = 7.0, 5.3$ Hz, 1H), 3.69 (s, 1H), 2.84 (m, 2H), 2.20 (s, 3H).$^{1,9,12}$

HPLC (ID column, 1 mL/min, 10% iso-propanol, 209 nm)
3. $^1$H NMR Titration of the P3 and T3 mixture with CuSO$_4$·5H$_2$O:

Spectra recorded on a Varian 400 MHz spectrometer at room temperature. TMS was added to THF-d8 to be used as reference signal. $^1$H NMR titration experiment was performed by gradual addition of CuSO$_4$·5H$_2$O (30 mM) + P3 (16 mM) + T3 (16 mM) in THF-d8 and 37% (v/v) D$_2$O to a solution of P3 (16 mM) and T3 (16 mM) in THF-d8.

Broad signals were observed after addition of CuSO$_4$·5H$_2$O. It indicates the presence of several species in fast exchange.
4. **$^1$H NMR Titration of P3 with CuSO$_4$·5H$_2$O:**

Spectra recorded on a Varian 400 MHz spectrometer at room temperature. TMS was added to THF-d8 to be used as reference signal. $^1$H NMR titration experiment was performed by gradual addition of CuSO$_4$·5H$_2$O (30 mM) + P3 (16 mM) in THF-d8 and D$_2$O (50% (v/v)) to a solution of P3 (16 mM) in THF-d8.

Relative broadening for peak 1: 4.05

Relative broadening for peak 2: 1.15

Relative broadening for peak 3: 2.21

These results suggest a preferential binding through the pyridine.
5. **EPR spectra:**

Electron paramagnetic resonance (EPR) spectra were recorded at room temperature. The CuSO$_4$·5H$_2$O solution was prepared at 2 mM in THF:H$_2$O (1:1). Other solutions were prepared at 2 mM of CuSO$_4$·5H$_2$O and 40 mM of P3 or T3 or P3/T3 in THF and 10 % (v/v) water and the mixture was stirred at room temperature.

![CuSO4 EPR spectrum](image1)

![CuSO4+P3 EPR spectrum](image2)
6. UV/VIS spectra of ligands P3, T3, and mixtures P3-T3 and CuSO$_4$·5H$_2$O-P3-T3:

A) 1) The CuSO$_4$·P3·T3 solution was prepared at 2 mM of CuSO$_4$·5H$_2$O, 40 mM of P3 and 40 mM of T3 in THF (spectroscopic grade) and 2.5 % (v/v) water. 100 µL of this solution was diluted to 4 mL THF (spectroscopic grade). Final concentration: 0.05 mM of CuSO$_4$·5H$_2$O, 1 mM of P3 and 1 mM of T3.

2) P3-T3 solution was prepared at 10 mM of P3 and 10 mM of T3 in THF (spectroscopic grade). 200 µL of this solution was diluted to 2 mL THF (spectroscopic grade). Final concentration: 1 mM of P3 and 1 mM of T3.

3) P3, T3 solutions were prepared at 10 mM in THF (spectroscopic grade). 200 µL of this solution was diluted to 2 mL THF (spectroscopic grade). Final concentration: 1 mM of P3 or T3.

UV-Vis absorbance measurements: In a UV-Vis cuvette, which contains 2 mL of THF, 20 µL of the corresponding solution was added.

UV-Vis spectroscopy did not show changes in the CuSO$_4$·P3·T3 absorption spectrum, which correspond to the sum of P3 and T3.

B) The CuSO$_4$·P3·T3 solution was prepared at 84 mM of CuSO$_4$·5H$_2$O, 840 mM of P3 and 840 mM of T3 in THF (spectroscopic grade) and 10 % (v/v) water. The CuSO$_4$·5H$_2$O was prepared at 84 mM in water. P3 and T3 solutions were prepared at 840 mM in THF.
7. Mass spectrometry (MALDI-TOF):

MALDI-TOF MS experiments were performed in positive and negative ion mode without matrix. Identified species with the corresponding calculated and recorded isotope distributions are showed.

A) Negative mode:

\[
[CuSO_4(H_2O)_3(P_3)(T_3)]+Na-H
\]

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[S17]
[CuSO₄(H₂O)₃(P₃H)(T₃)-H]
$[\text{CuSO}_4(H_2O)_3(P3H)(P3)+\text{Na}]^+$

- **Found**
  - Intensity (%)
  - Mass (m/z)
  - Peaks at 619.1, 620.1, 621.1, 622.1, 623.1

- **Calculated**
  - Peaks at 619.1, 620.1, 621.1, 622.1, 623.1

$[\text{CuSO}_4(H_2O)_3(P3H)(T3)+\text{Na}]^+$

- **Found**
  - Intensity (%)
  - Mass (m/z)
  - Peaks at 793.0, 794.0, 795.0, 796.0, 797.0

- **Calculated**
  - Peaks at 793.1, 794.1, 795.1, 796.1, 797.1
8. Non-linear effect (NLE) studies:

A mixture of CuSO$_4$·5H$_2$O (0.92 mg, 3.7·10$^{-3}$ mmol, 1 mol %), P$_3$ (S-P$_3$ was combined with R-P$_3$ in appropriate ratios) (14 mg, 0.074 mmol, 20 mol %) and T$_3$ (27 mg, 0.074 mmol, 20 mol %) was stirred in dry THF (528 µL) and H$_2$O (13 µL, 1.1 mmol respect to p-nitrobenzaldehyde) at room temperature for 1 h. Then, the p-nitrobenzaldehyde (56 mg, 0.37 mmol) and cyclohexanone (383 µL, 3.7 mmol) were added. The reactions were sampled at different conversions and analyzed by chiral HPLC to determine the ee of product.

![Graph showing ee (%) catalyst vs. ee (%) product for 83% conversion.](image1)

![Graph showing ee (%) catalyst vs. ee (%) product for 100% conversion.](image2)
9. **Experiment with CuCl+Ag$_2$SO$_4$ under inert atmosphere:**

The aldol reaction of cyclohexanone and p-nitrobenzaldehyde was studied using 2 mol% CuCl, 1 mol% Ag$_2$SO$_4$, 20 mol% P3 and 20 mol% U3 in THF plus 2 equiv. water, at rt. A clearly slower and less enantioselective reaction was obtained.

<table>
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<th>Time [h]</th>
<th>Conversion [%]</th>
<th>d.r.(anti/syn)</th>
<th>ee% (anti)</th>
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<td>24</td>
<td>91:9</td>
<td>n.d.</td>
</tr>
<tr>
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</tr>
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<td>21</td>
<td>99</td>
<td>90:10</td>
<td>89</td>
</tr>
</tbody>
</table>

The aldol reaction of cyclohexanone and p-nitrobenzaldehyde was studied using 2 mol% CuCl, 1 mol% Ag$_2$SO$_4$, 20 mol% P3 and 20 mol% U3 in THF plus 2 equiv. water, at rt. A clearly slower and less enantioselective reaction was obtained.

10. **Thiourea (T3) vs. urea (U3) ligands under Cu(I)-sulfate catalysis.**

Essentially identical results are obtained compared to the reaction run under open air conditions. This proofs no effect of air in the potential oxidation of thiourea ligands.
11. NMR spectra of pyridine ligands and intermediates:

Z-P2:
P2:
P3:

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{H}
\end{align*}
\]
Z-P4:

![Chemical Structure](image)

![NMR Spectrum](image)
P4:

![NHNHO](image1)

![NHNHO](image2)
T3:

Chemical structures and spectra are shown. The spectra include peaks at various ppm values.
11. References: