SUPPORTING INFORMATION

FOR

A DEGENERATE METAL-TEMPLATED CATALYTIC SYSTEM WITH REDUNDANT FUNCTIONAL GROUPS FOR THE ASYMMETRIC ALDOL REACTION

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1. **SYNTHESIS AND CHARACTERIZATION OF DI-5,5'-PROLINAMIDO-2,2'-BIPYRIDINE 9 (bipyPro2)**

![Scheme S1. Coupling between bipyridine 8 and Boc-proline.](image)

In a flame-dried flask, D-Boc-proline (508.6 mg, 2.36 mmol, 2.2 eq) was dissolved in dry THF (8 mL) under N₂. At 0 °C, Et₃N (600 μL, 4.30 mmol, 4 eq) and ClCO₂Et (409 μL, 4.30 mmol, 4 eq) were successfully added. The mixture was stirred at 0 °C for 30 minutes. Afterwards, the diaminobipyridine 8 was added (200 mg, 1.07 mmol, 1 eq) and the mixture further stirred at 0 °C for 30 minutes, at rt for 2 h and at 70 °C in an aluminum block overnight. After cooling to rt, the mixture was diluted with EtOAc, filtered and solvents were removed in a rotatory evaporator. The crude product was purified by silica gel column chromatography using a gradient of DCM (100 – 93 %) / MeOH (NH₃ 1 N) (0 – 7 %) to give 200 mg of Boc-protected 9 (32% yield)

**¹H-NMR (400 MHz, DMSO-d₆)** δ 10.35 (s, 2H), 8.82 (dd, J = 12.5, 2.5 Hz, 2H), 8.28 (dd, J = 8.7, 3.9 Hz, 2H), 8.17 (dd, J = 8.7, 2.8 Hz, 2H), 4.36 – 4.17 (m, 2H), 4.17 – 4.01 (m, 2H), 3.52 – 3.33 (m, 2H), 2.29 – 2.10 (m, 2H), 1.91 – 1.79 (m, 6H), 1.40 – 1.27 (m, 18H) ppm.

**HRMS (ESI-TOF) calcd. for C₃₀H₄₁N₆O₆⁺ [M+H]+ (m/z): 581.3082, found: 581.3085**

![Scheme S2. Boc-group deprotection leading to ligand bipyPro₂ (compound 9).](image)

1.10 g (1.89 mmol, 1 eq) of Boc-protected 9 was dissolved in a mixture of dry DCM (11.34 mL) and TFA (3.78 mL). Then, 4.65 mL of triisopropylsilane were added and the mixture further stirred at rt for 2 h. Then, the liquids were evaporated and the resulting product was washed with Et₂O, dissolved with water and lyophilized. The obtained powder was purified by reversed-phase chromatography using a gradient of H₂O (100 – 0 %) – ACN (0 – 100%). The fraction containing the product was collected and the solvents were evaporated. Then, the obtained powder was dissolved in CHCl₃ and a solution of NaOH 2 M was added to make the solution weakly alkaline. Afterwards, the solution was extracted with CHCl₃ (3 × 50 mL) and the combined organic extracts were dried over anhydrous Na₂SO₄. The solvent was removed with a rotatory evaporator to afford 124 mg of 9 (56 % yield)

**¹H NMR (400 MHz, CDCl₃)** δ 9.94 (s, 2H), 8.70 (t, J = 1.6 Hz, 2H), 8.30 (d, J = 1.6 Hz, 4H), 3.90 (dd, J = 9.3, 5.2 Hz, 2H), 3.07 (ddt, J = 38.3, 10.3, 6.5 Hz, 4H), 2.34 – 1.96 (m, 4H), 1.91 – 1.72 (m, 10H), 1.40 – 1.22 (m, 2H) ppm.
$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$) δ 174.1 (Cq), 151.3 (Cq), 140.1 (CH), 134.4 (Cq), 126.4 (CH), 120.9 (CH), 61.0 (CH), 47.4 (CH$_2$), 30.8 (CH$_2$), 26.4 (CH$_2$) ppm.

HRMS (ESI-TOF) calcd. for C$_{20}$H$_{25}$N$_6$O$_2$ $^+$ [M+H]$^+$ (m/z): 381.2034, found: 381.2018.

$[\alpha]_D^{25}$ $^\circ$ +79.2 (c=0.5, MeOH).
tert-butyl-(S)-2-((5′-(R)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido)-[2,2′-bipyridin]-5-yl)carbamoyl)pyrrolidine-1-carboxylate.

$^1$H NMR (400 MHz, DMSO-d$_6$):

**Figure S1.** $^1$H NMR spectrum of Boc-protected bipyPro$_2$. 

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di-5,5’-prolinamido-2,2’-bipyridine 9 (bipyPro₂).

\(^1\)H NMR (400 MHz, MeOD):

Figure S2. \(^1\)H NMR spectrum of bipyPro₂.
di-5,5’-prolinamido-2,2’-bipyridine 9 (bipyPro$_2$).

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$):

Figure S3. $^{13}$C($^1$H) NMR spectrum of bipyPro$_2$. 
2. **SYNTHESIS AND CHARACTERIZATION OF 2,2'-BIPYRIDYL-5,5'-DIHYDROXAMIC ACID 4**

Procedure adapted from Eur. J. Med. Chem. 2019, 178, 116-130.[1]

Scheme S3. Synthesis of dihydroxamic acid 4.

2,2'-bipyridyl-5,5'-dicarboxylate methyl ester (272 mg, 1 mmol) was dissolved in 3 ml CH$_2$Cl$_2$ and 6 ml MeOH and cooled to 0 °C. Then, hydroxylamine (4 ml 50% in water, 60 mmol) and sodium hydroxide (160 mg, 4 mmol) were added. The reaction was stirred at 0 °C and left reacting overnight while warming up to rt. A bright yellow precipitate is formed. Ethanol was added and the mixture filtered. The precipitate was washed with ethanol and dried, furnishing 275 mg of dihydroxamic acid 4 (quantitative yield).
$^1$H NMR (400 MHz, DMSO-$d^6$) of 4:

Figure S4. $^1$H NMR spectrum of dihydroxamic acid 4.
3. **SYNTHESIS AND CHARACTERIZATION OF 2,2'-BIPYRIDYL-5,5'-DIBENZYLAMIDE 5[2]**

Described in ref. [2].

![Scheme S4.](image)

$^1$H NMR (400 MHz, DMSO-$d_6$) of 5:

![Figure S5. $^1$H NMR spectrum of diamide 5.](image)
4. SPECTRA OF LIGANDS AND INTERMEDIATES [3]
Synthesized according to ref. [3]

2,2'-bipyridine-5,5'-dicarboxylic acid (2):

\[^1\text{H} \text{NMR (400 MHz, DMSO-d}^6\text{)}:\]

![Figure S6. \[^1\text{H} \text{NMR spectrum of dicarboxylic acid 2.}]

Figure S6. \[^1\text{H} \text{NMR spectrum of dicarboxylic acid 2.}
Diethyl 2,2’-bipyridine-5,5’-dicarboxylale (3):

$^1$H NMR (400 MHz, DMSO-$d^6$):

Figure S7. $^1$H NMR spectrum of diester 3.
2,2′-bipyridine-5,5′-dicarbohydrazide (6).

$^1$H NMR (400 MHz, DMSO-d$_6$) of 6:

**Figure S8.** $^1$H NMR spectrum of dihydrazide 6.
**Figure S9.** $^1$H NMR spectrum of diacylazide 8.
FTIR(ATR) of 8:

Figure S10. FTIR spectrum of diacylazide 8.
Diethyl 2,2’-bipyridine-5,5’-diyldicarbamate (7):

$^1$H NMR (400 MHz, DMSO-d$^6$) of 7:

![NMR Spectrum](image)

**Figure S11.** $^1$H NMR spectrum of dicarbamate 7.
2,2'-bipyridine-5,5'-diamine (9):

$^1$H NMR (400 MHz, DMSO-d$^6$) of 9:

![NMR spectrum](image)

**Figure S12.** $^1$H NMR spectrum of bipyridine diamine 9.
5. PROCEDURE FOR THE ASYMMETRIC ALDOL REACTION AND ee DETERMINATION [4]

A mixture of the three catalyst components was stirred in 300 μL of dry THF and 10 μL of H₂O for 1 h. Then, 90 mg of p-nitrobenzaldehyde (0.595 mmol, 1 eq) and 617 μL of cyclohexanone (5.95 mmol, 10 eq) were added. When the reaction finished, H₂O was added and the solution was extracted with EtOAc. The organic phase was dried over anhydrous MgSO₄, filtered and the solvents evaporated in the rotavap. The crude product was purified by silica gel column chromatography using a gradient of Hexane (100 – 50 %) / EtOAc (0 – 50 %) to give 110 mg of the aldol product (74 % yield). Chiral analysis was performed using a Chiralpak IB column eluting with n-hexane / isopropanol (90/10) mobile phase, flow 1 mL/min, 30 minutes.

^1H-NMR (400 MHz, CDCl₃) δ 8.25 – 8.17 (m, 2H), 7.55 – 7.46 (m, 2H), 4.90 (d, J = 8.3 Hz, 1H), 4.31 – 3.75 (m, 1H), 2.59 (dddd, J = 13.9, 8.4, 5.5, 1.2 Hz, 1H), 2.54 – 2.45 (m, 1H), 2.36 (tdd, J = 13.6, 6.2, 1.2 Hz, 1H), 2.11 (ddt, J = 12.2, 5.8, 3.0 Hz, 1H), 1.91 – 1.80 (m, 1H), 1.67 (dt, J = 13.0, 3.8 Hz, 1H), 1.58 (ddt, J = 13.3, 10.0, 3.3 Hz, 2H), 1.45 – 1.31 (m, 1H) ppm.

Figure S13. HPLC determination of enantiomeric excess.

For details and analyses on the other aldol products, see our previous publications.[4]
6. **EFFECT OF SOLVENTS IN CONVERSION AND STEREOSELECTIVITY**

![Chemical reaction diagram]

| Entry | Solvent | Conv. [%] | d.r. (anti/syn) | ee [%] |
|-------|---------|-----------|-----------------|--------|
| 1     | THF     | 100       | 8/1             | 95     |
| 2     | DMSO    | 92        | 4/1             | 83     |
| 3     | DMF     | 98        | 5/1             | 92     |
| 4     | ACN     | 74        | 5/1             | 94     |

*Table S1*. Effect of solvents in conversion and stereoselectivity.
7. DETERMINATION OF APARENT KINETIC CONSTANTS

Conversion vs. time plot for the aldol reaction between cyclohexanone and $p$-nitrobenzaldehyde, at rt. Fitting was performed with Origin software.

A) 5 mol% Zn(TFA)$_2$+bipyPro$_2$+bipyHA$_2$. $k_{ap} = 1/t_1 = 0.474$ h$^{-1}$

B) 5 mol% Zn(TFA)$_2$+bipyPro$_2$. $k_{ap} = 1/t_1 = 0.257$ h$^{-1}$

Figure S14. Conversion vs. time fitting and determination of apparent kinetic constants.
8. DETERMINATION OF CATALYST ORDER [5]

The graphical procedure developed by J. Burés was used.[5] Reaction of cyclohexanone and \( p \)-nitrobenzaldehyde at rt with different catalyst loadings (1, 2 and 5 mol% of \( \text{Zn(TFA)}_2 + \text{bipyPro}_2 + \text{bipyHA}_2 \)) was sampled and conversion determined by \(^1\)H NMR. From there, \([p\text{-nitrobenzaldehyde}]\) vs. time plots were constructed:

Graphical fitting of different options concluded that the order of catalyst was 1:

![Graphs showing orders 1/2, 1, and 2 for catalyst determination.]

**Figure S15.** Determination of catalyst order for \( \text{Zn(TFA)}_2 + \text{bipyPro}_2 + \text{bipyHA}_2 \).
Since three different zinc complexes with two ligands can arise from a 1:1:1 mixture of Zn:bipyPro₂:bipyHA₂, ranging from the statistical 25:50:25 distribution to 100% Zn[bipyPro₂]₂(bipyHA₂), the validity of the catalyst order calculation could be challenged. However, firstly, we had found that the equilibrium constant formation for our previous bipyridine based ZnL₁L₂ complex was \(3.5 \times 10^{11} \text{ M}^{-1}\), whereas the Zn(L₁)₂ and Zn(L₂)₂ equilibrium constants were \(4 \times 10^{10}\) and \(1 \times 10^{11} \text{ M}^{-1}\), in line with the literature. These values led to the predominant formation of 71% ZnL₁L₂, and 14% of Zn(L₁)₂ and Zn(L₂)₂ each, overcoming the statistical distribution.[4c]

Secondly, as a consequence of these large formation constants the zinc complexes distribution does not change, whatever it is, at least in the range of concentrations used for catalysis (from 4 to 20 mM). This is, the different zinc complexes are not under real reversible equilibrium. See Figure S16 below.

Finally, since the catalyst order determination is therefore not affected by the real concentration of catalyst, which remains proportional to the amount introduced initially into the reaction, we have used for the catalyst order determination the weighed molar amount of the different components.

![Figure S16](attachment:image.png)

**Figure S16.** Species distribution for a Zn complex with two bipyridine ligands in the range 4 to 20 mM with \(K_{eq} = 3.5 \times 10^{11} \text{ M}^{-1}\) (Zn[bipyPro]₁(bipyTU); ABC), \(4 \times 10^{10} \text{ M}^{-1}\) (Zn[bipyPro]₂; AB₂) and \(1 \times 10^{11} \text{ M}^{-1}\) (Zn[bipyTU]₂; AC₂). Plotted from data in ref. 4c using HySS software.
9. DETERMINATION OF CATALYST TOF

First, NMR conversion vs. time data was obtained through sampling the corresponding aldol reactions between cyclohexanone and p-nitrobenzaldehyde at rt, using 5 mol% of both catalytic systems (Zn(TFA)$_2$+bipyPro+bipyTU [old system] vs. Zn(TFA)$_2$+bipyPro$_2$+bipyHA$_2$ [new system]). Then, a [p-nitrobenzaldehyde] vs. time plot was constructed. Data points were fitted to polynomial equations:

Figure S17. Fitting curves for [p-nitrobenzaldehyde] vs. time for the current (blue dots) and previous (red dots) catalytic systems.

These equations were derived to obtain rate equations, which furnished the TOF for each catalyst upon division by the ligand (bipyPro or bipyPro$_2$) concentration:

Figure S18. Calculated TOF vs. time curves for the current (blue dots) and previous (red dots) catalytic systems.

From this plot, initial TOF’s were found:

TOF$_0$[bipyPro$_2$] = 11 h$^{-1}$
TOF$_0$[bipyPro] = 2.2 h$^{-1}$
For comparison, since \textit{bipyPro}_2 has double the catalytic sites than \textit{bipyPro}, TOF[\textit{bipyPro}_2] must be divided by 2 (11 / 2 = 5.5 h\(^{-1}\) vs. 2.2 h\(^{-1}\) from \textit{bipyPro}), or alternatively, TOF[\textit{bipyPro}] must be multiplied by 2 (2.2 x 2 = 4.4 h\(^{-1}\) vs. 11 h\(^{-1}\) from \textit{bipyPro}_2). In any case, the catalytic system containing \textit{bipyPro}_2 is significantly faster. Indeed, the system Zn(TFA)\(_2\)+\textit{bipyPro}_2+\textit{bipyHA}_2 is 5 times faster, not twice faster as it could be expected by doubling the number of catalytic sites in the ligand.
This proposed mechanism must be understood as based on current and previous research of our group.[4c] Please, keep in mind that it is a speculative mechanism lacking comprehensive kinetic and theoretical studies. It is presented herein to give the vision of the authors on the catalyst operation (Please, check also Sections 8 and 9 in this Supporting Information). We propose a working mechanism in which a predominant zinc-templated bifunctional catalyst behaves as the catalytically most active species. The Zn(bipyPro2)(bipyHA2) complex would work via an enamine mechanism with cyclohexanone using one prolinamide moiety and attract the aldehyde through hydrogen bonding through one of the hydrazide groups. In this way the asymmetric aldol reaction could take place in a stereocontrolled fashion. The observed diastereo- and enantioselectivity can be rationalized in this way too.

\[
\text{Zn}^{2+} + \text{bipyPro}_2 + \text{bipyHA}_2
\]

\[
\text{Zn(bipyPro}_2)_2 + \text{Zn(bipyHA}_2)_2 \rightarrow \text{Zn(bipyPro}_2)(\text{bipyHA}_2)
\]

Figure S19. Simplified mechanistic proposal and model for the observed stereoselectivity.
Figure S20. Views (images A-F) of the transition state model for the asymmetric aldol reaction of cyclohexanone and benzaldehyde. Most hydrogen atoms have been omitted for clarity. The bipyridine-zinc complex with non-reacting functional groups is shown in tube model. The reacting functional groups with cyclohexanone enamine and benzaldehyde are shown in ball and spoke model: Grey, carbon; Red, oxygen; Blue, nitrogen; White, hydrogen.
13. REFERENCES

[1] Z. Yang, M. Shen, M. Tang, W. Zhang, X. Cui, Z. Zhang, H. Pei, Y. Li, M. Hu, P. Bai, L. Chen. Discovery of 1,2,4-oxadiazole-Containing hydroxamic acid derivatives as histone deacetylase inhibitors potential application in cancer therapy. *Eur. J. Med. Chem.* **2019**, *178*, 116-130

[2] S. Saha, S. Santra, P. Ghosh. Cu²⁺-Templated Threading of a Bis-amide-tris-amine Macrocycle by Substituted 2,2'-Bipyridyl Derivatives Assisted by Strong π–π Stacking and Second-Sphere H-Bonding Interactions. *Eur. J. Inorg. Chem.* **2014**, *2029*-2037.

[3] (a) Janiak, C.; Deblon, S.; Wu, H.-P. Syntheses of 5,5’-Disubstituted 2,2’-Bipyridines. *Synth. Commun.*, **1999**, *29*, 3341-3352. (b) Janiak, C.; Deblon, S.; Wu, H.-P.; Kolm, M. J.; Klufers, P.; Piotrowski, H.; Mayer, P. Modified Bipyridines: 5,5’-Diamino-2,2’-bipyridine Metal Complexes Assembled into Multidimensional Networks via Hydrogen Bonding and π–π Stacking Interactions. *Eur. J. Inorg. Chem.*, **1999**, *1507*-1521

[4] (a) A. Serra-Pont, I. Alfonso, C. Jimeno and J. Solà. Dynamic assembly of a zinc-templated bifunctional organocatalyst in the presence of water for the asymmetric aldol reaction. *Chem. Commun.*, **2015**, *51*, 17386-17389. (b) A. Serra-Pont, I. Alfonso, J. Solà and C. Jimeno. A copper-templated, bifunctional organocatalyst: a strongly cooperative dynamic system for the aldol reaction. *Org. Biomol. Chem.*, **2017**, *15*, 6584-6591. (c) A. Serra-Pont, I. Alfonso, J. Solà and C. Jimeno. An efficient dynamic asymmetric catalytic system within a zinc-templated network. *Chem. Commun.*, **2019**, *55*, 7970-7973. (d) A. M. Valdivielso, A. Catot, I. Alfonso and C. Jimeno. Intramolecular hydrogen bonding guides a cationic amphiphilic organocatalyst to highly stereoselective aldol reactions in water. *RSC Adv.*, **2015**, *5*, 62331-62335.

[5] (a) J. Burés. A Simple Graphical Method to Determine the Order in Catalyst. *Angew. Chem. Int. Ed.*, **2016**, *55*, 2028-2031. (b) C. D. T. Nielsen and J. Burés. Visual kinetic analysis. *Chem. Sci.*, **2019**, *10*, 348-353