Supplementary Information

Dynamic Multi-Component Covalent Assembly for the Reversible Binding of Secondary Alcohols and Chirality Sensing

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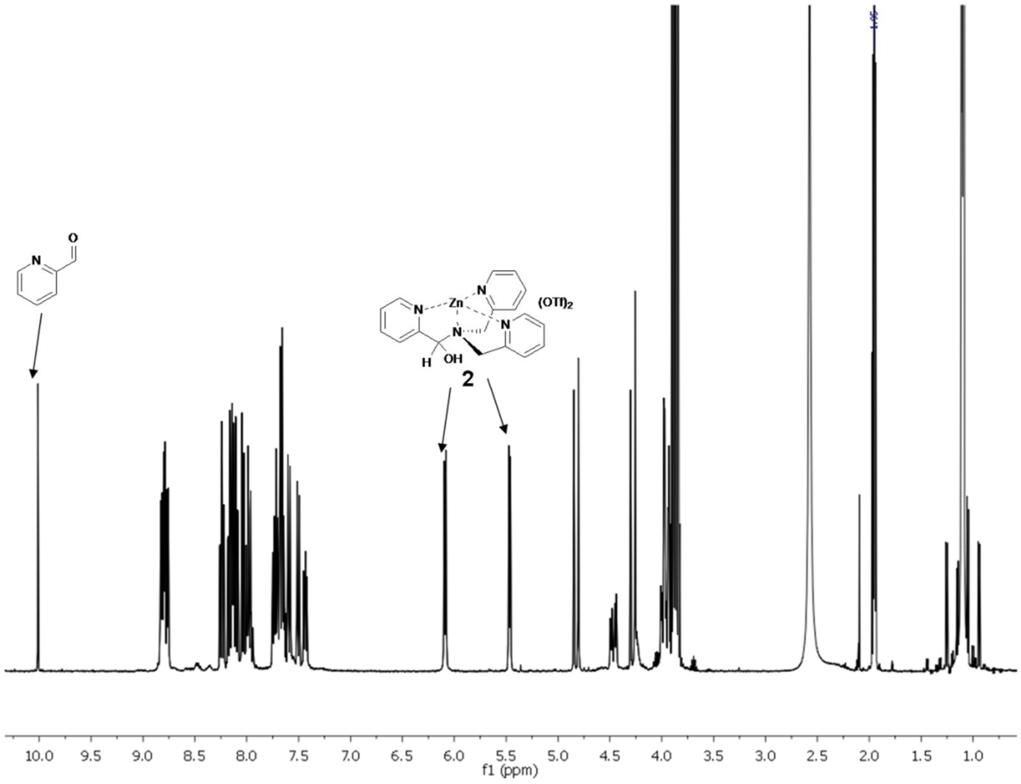
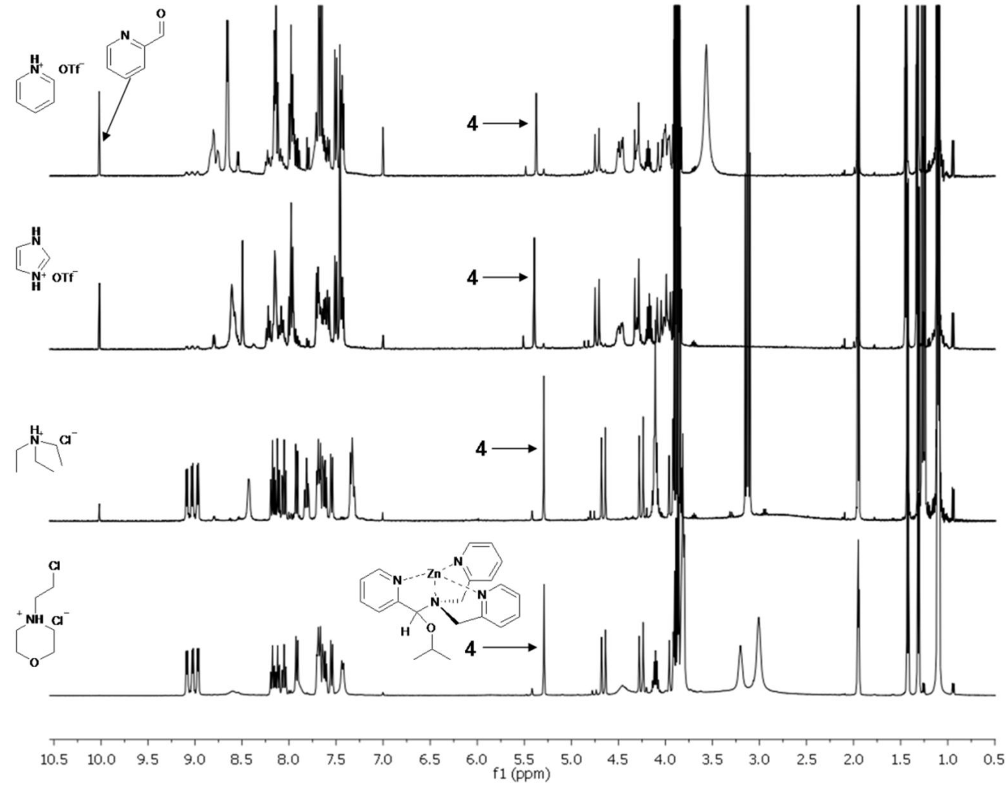
General. NMR spectra were recorded at The University of Texas at Austin NMR facility. ESI-mass spectra were obtained at The University of Texas at Austin mass spectrometry facility. Circular dichroism (CD) spectra were recorded on a Jasco J-815 spectropolarimeter at The Texas Institute of Drug and Diagnostic Development. All reagents were of the best grade commercially available from Sigma-Aldrich or Acros Organics.

Multi-component assembly and dyanmics. All assembly reactions were performed *in situ* in acetonitrile without isolation and purification. To a stirred solution of pyridine-2-carboxyaldehyde (**2-PA**, 30-40 mM, 1 equiv.) and zinc triflate ($Zn(OTf)_2$, 1 equiv.) in acetonitrile, were added activated 3Å molecular sieves (4 to 8 mesh), di-(2-picolyl)amine (**DPA**, 1.2 equiv.), a mono-ol (2- 5 equiv.), and 4-(2-chloroethyl)morpholine hydrochloride (CEM-HCl, 1 equiv.). The mixture was stirred at room temperature overnight. The assembly solution was characterized by ^{1}H NMR and ESI mass spectrometry. For model studies and screening, 5 equiv. of 2-propanol was used. For component exchange experiments, the assembly was conducted with one alcohol or aldehyde as described, and the second alcohol or aldehyde was then added and the mixture was stirred overnight. For chiral alcohols, diastereomers were generated, and the diastereomeric ratios (*dr*) were calculated using integrals in ^{1}H NMR spectra. For other experiments, see the related figure captions for details.

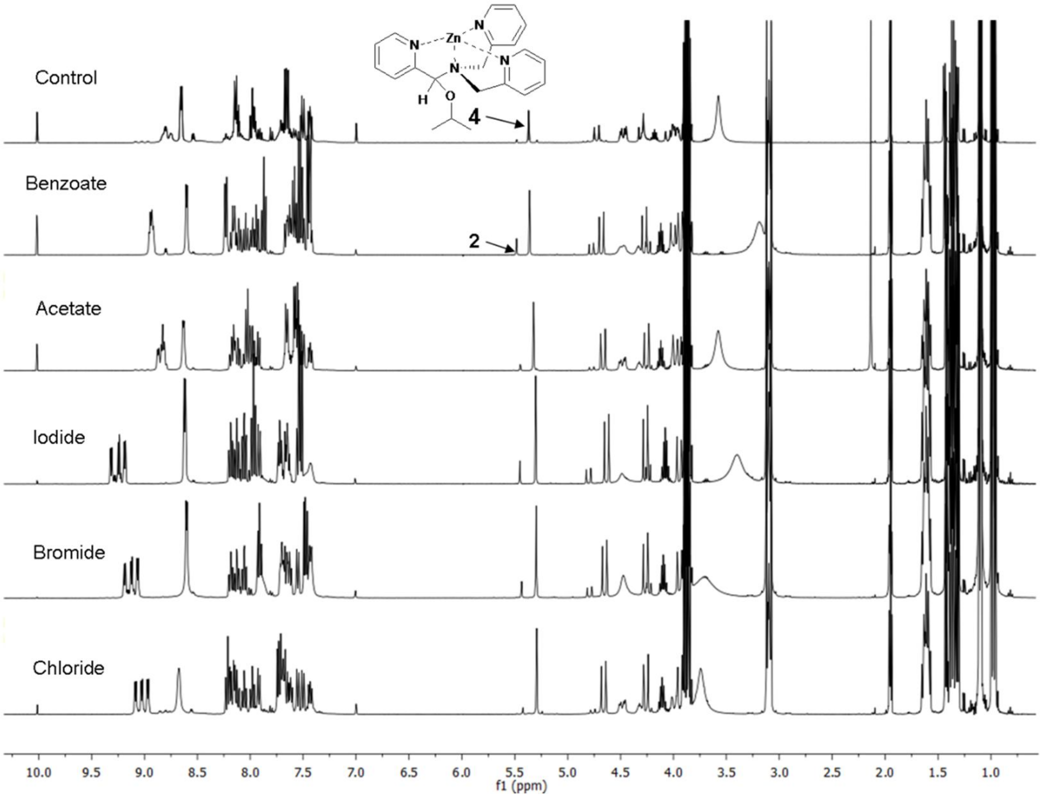
CD Studies. For CD analysis, the multi-component assemblies were conducted as described above with 35 mM of **2-PA**, and the CD spectra was recorded at 25 °C using a diluted solution (0.175 mM of **2-PA**, 1 cm cell). For enantiomeric excess (*ee*) analysis, 3 equiv. of 1-phenylethanol with varied *ee* values (-100, -80, -60, -40, -20, 0, 20, 40, 60, 80, 100%) were used for construction of calibration lines. Each data point was the average of three independent assembly reactions. The *ee* values of test samples were calculated using the corresponding calibration line, and the average error was calculated.



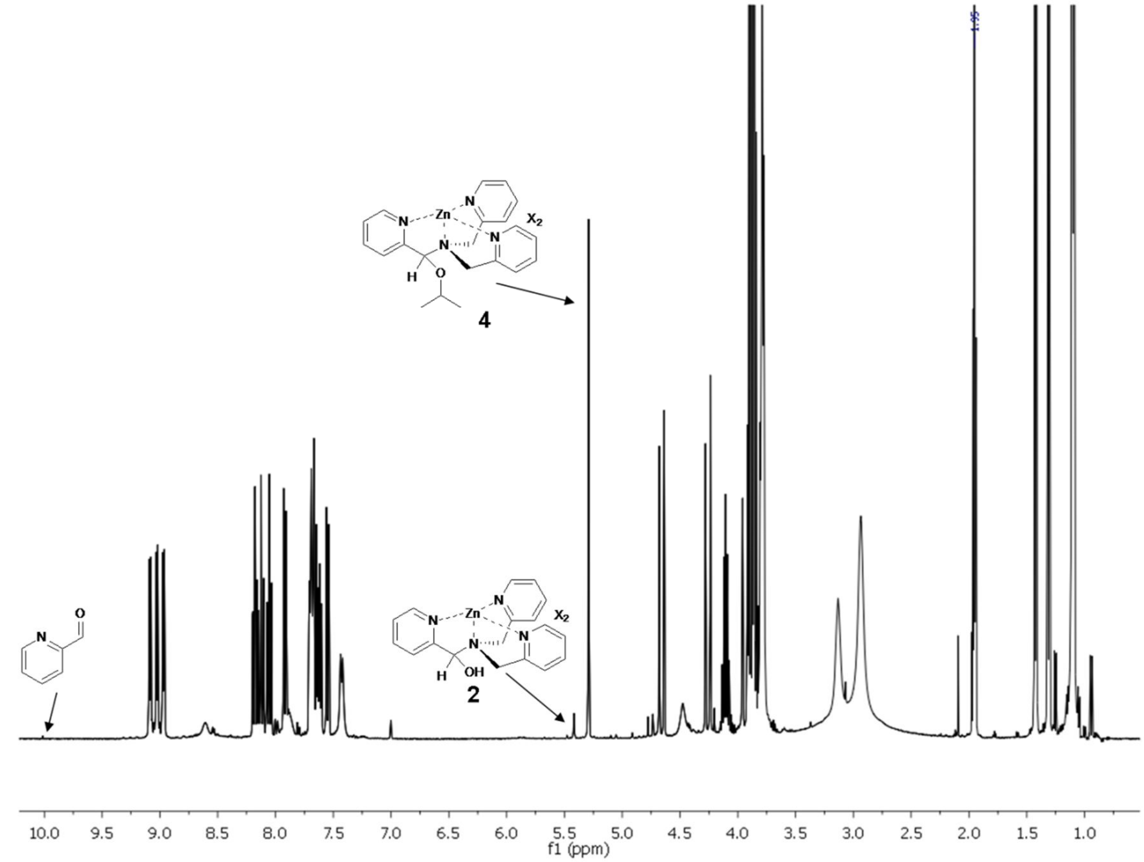
Supplementary Figure S1. ^{1}H NMR of the four-component assembly from 2-propanol without Brønsted acids. Due to coupling between CH and OH on the methine carbon, two doublets were observed.



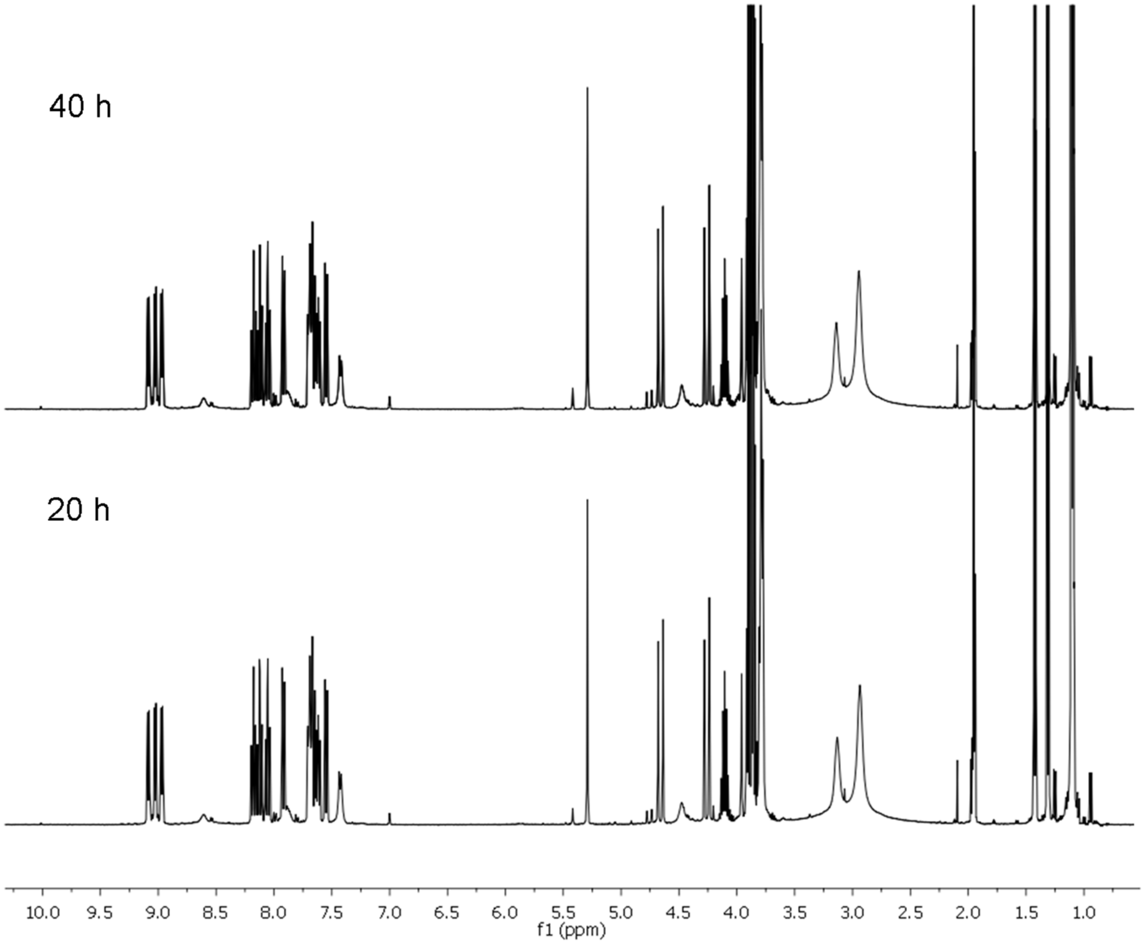
Supplementary Figure S2. ^{1}H NMR of the four-component assembly from 2-propanol with various Brønsted acids. The structure of the acids is shown in the figure. The small singlet around 5.4 ppm is methine CH of complex **2**. CH-OH coupling was not observed because acids were present in the mixture.



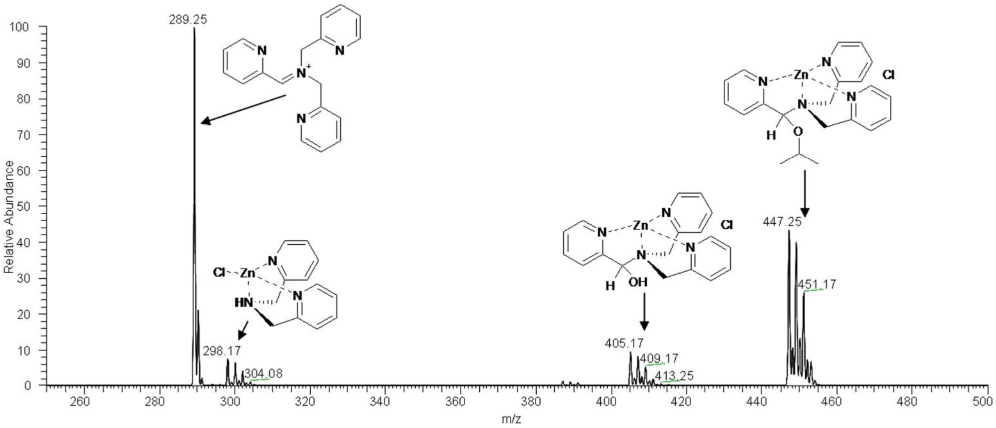
Supplementary Figure S3. ^{1}H NMR of the four-component assembly from 2-propanol in the presence of pyridinium triflate (control) with various tetrabutylammonium salts.



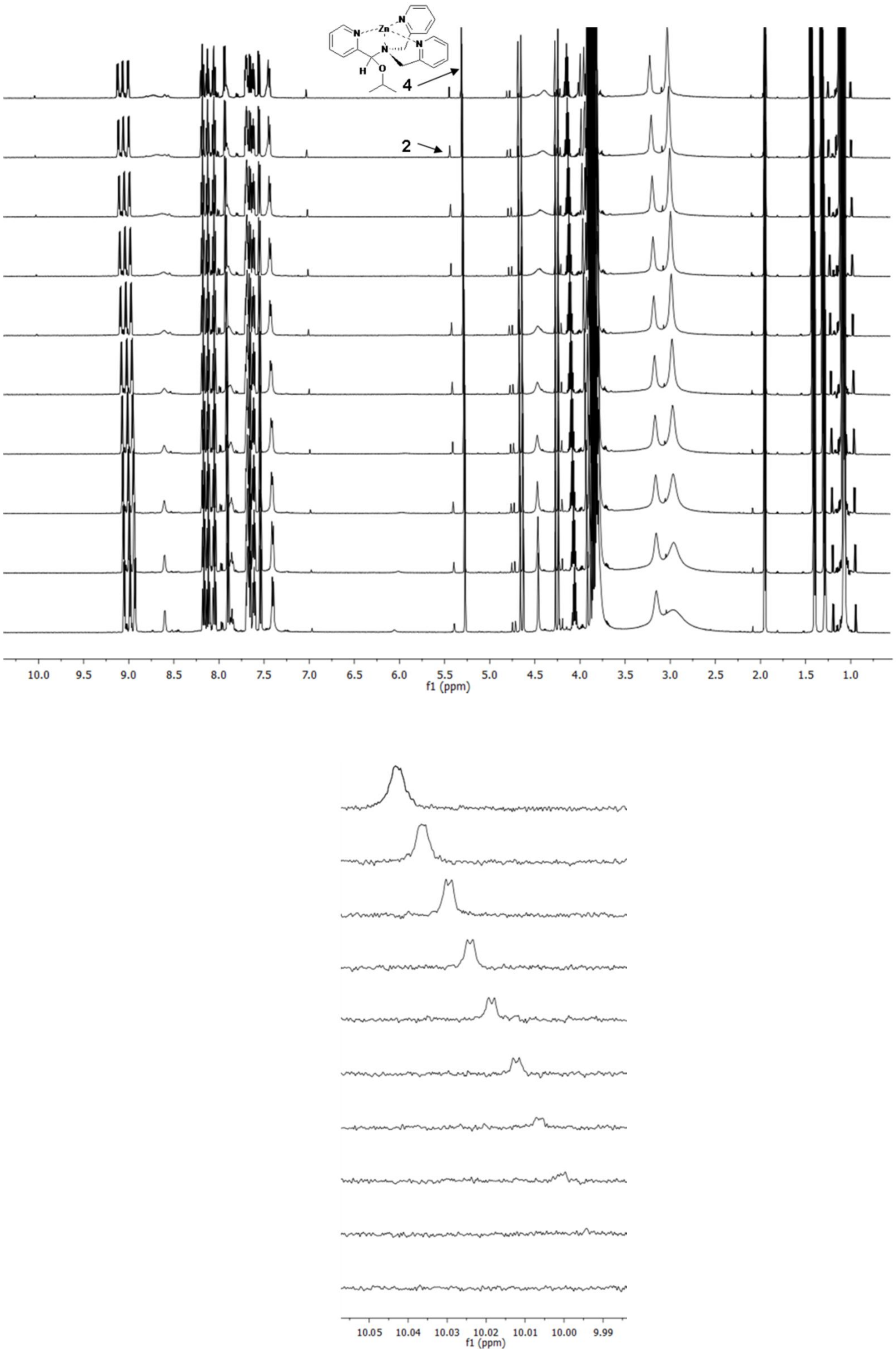
Supplementary Figure S4. ^{1}H NMR of the four-component assembly from 2-propanol with 4-(2-chloroethyl)morpholine hydrochloride (CEM-HCl). Only residue **2-PA** as well as **2** was detected.



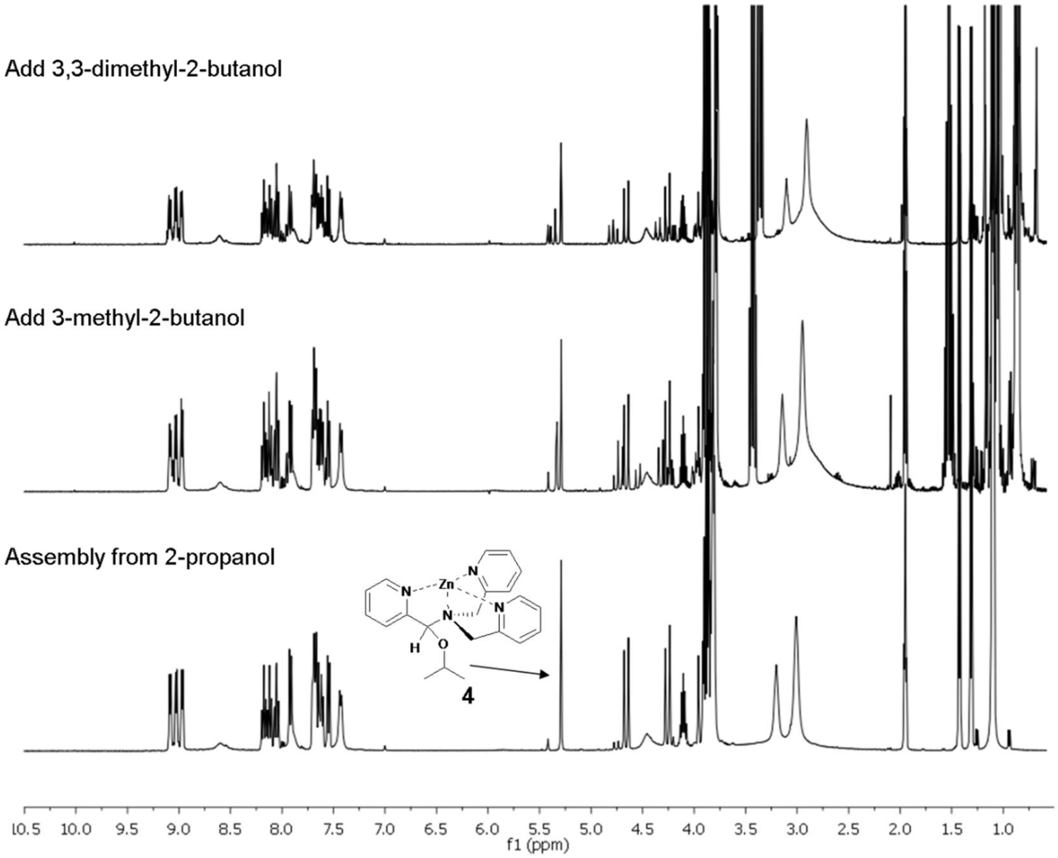
Supplementary Figure S5. ^{1}H NMR of the four-component assembly from 2-propanol with CEM-HCl after 20 h (bottom panel) and 40 h (top panel).



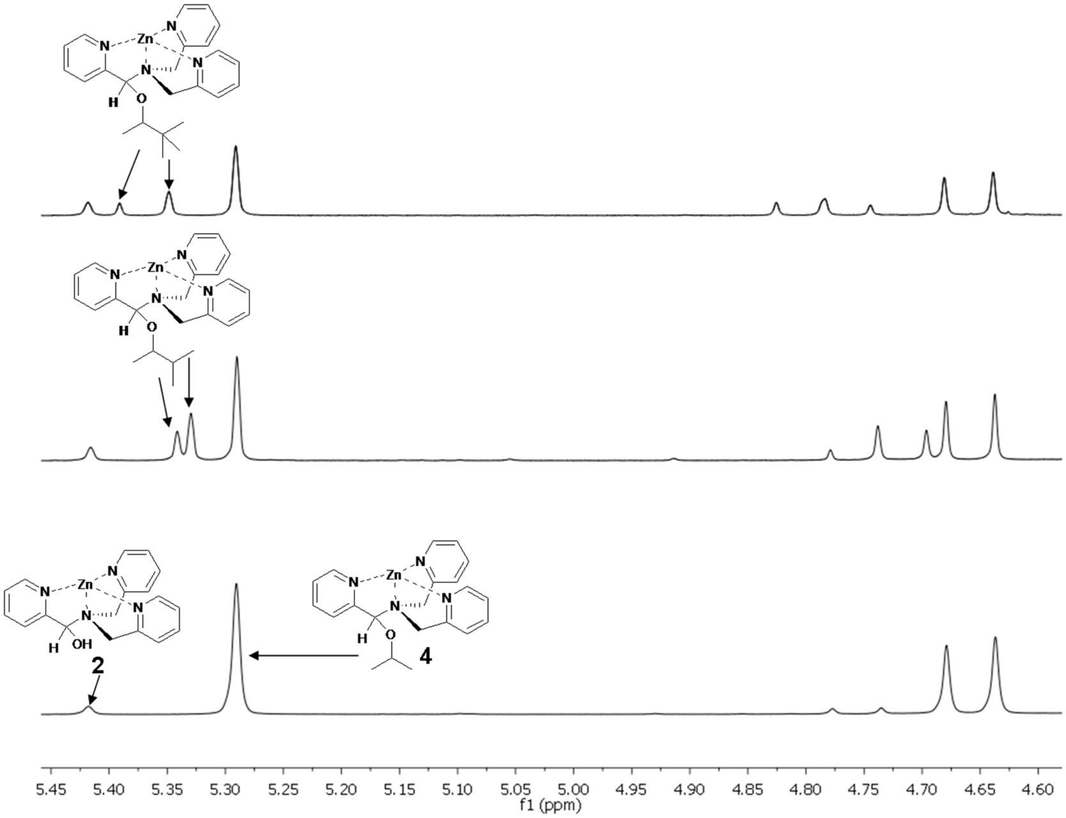
Supplementary Figure S6. ESI mass spectrum of the four-component assembly from 2-propanol with CEM-HCl.



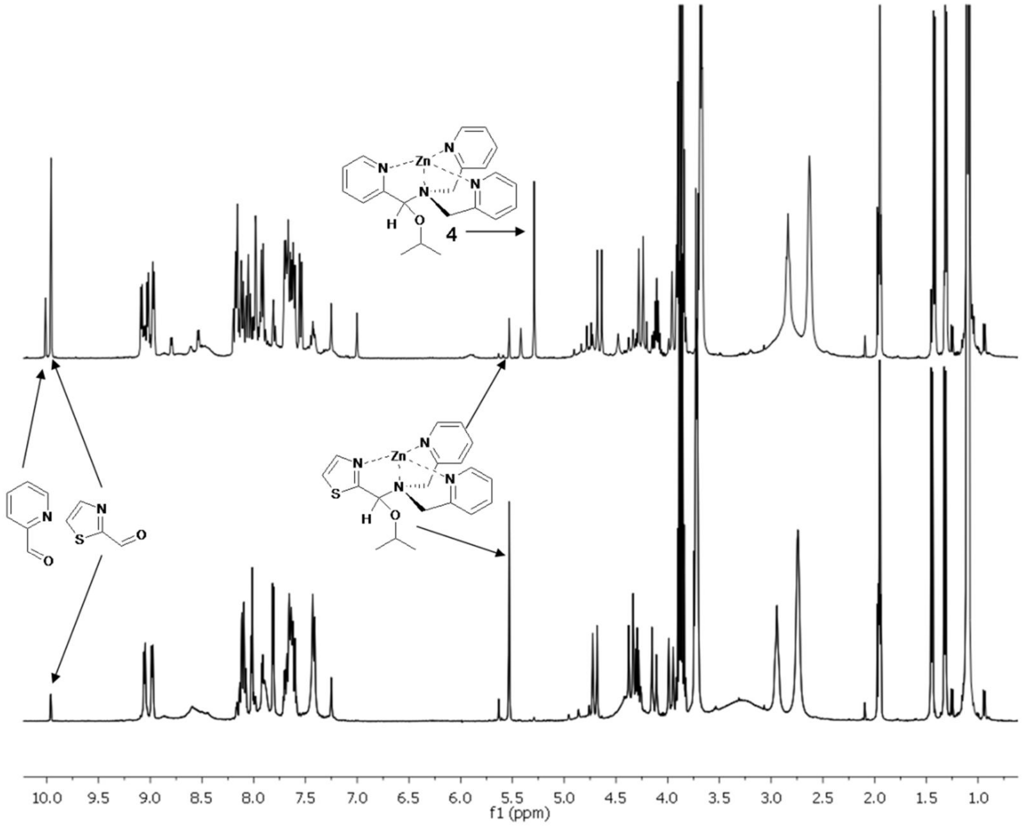
Supplementary Figure S7. ^{1}H NMR of the preformed four-component assembly from 2-propanol with CEM-HCl at various temperatures (from bottom to top: -20, -10, 0, 10, 20, 30, 40, 50, 60, 70 °C, top panel) and the expanded **2-PA** peak around 10 ppm (bottom panel).



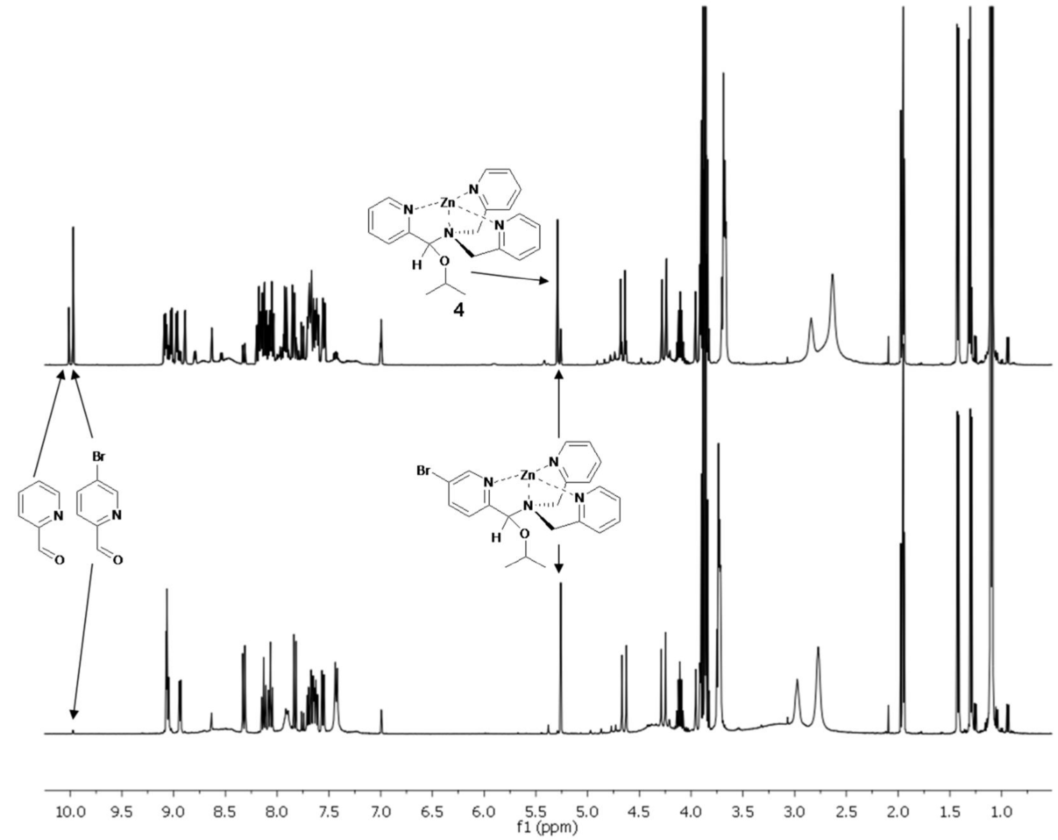
Supplementary Figure S8. ^{1}H NMR of the four-component assembly from 2-propanol with CEM-HCl (bottom panel), after addition of 3-methyl-2-butanol (middle panel), after addition of 3,3-dimethyl-2-butanol (top panel). Exchange of alcohols was observed, indicating that the assembly is reversible.



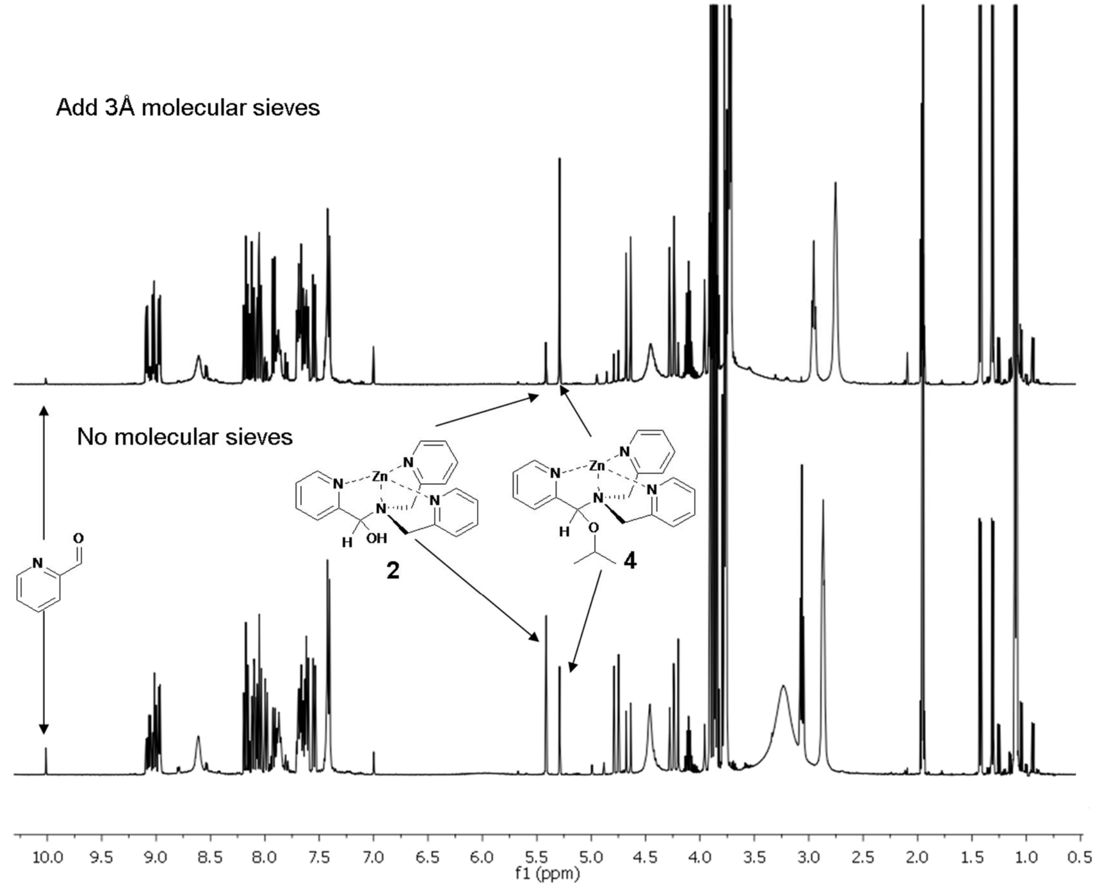
Supplementary Figure S9. Expanded region of ^{1}H NMR in Figure S9. In the case of 3-methyl-2-butanol (middle panel) and 3,3-dimethyl-2-butanol (top panel), diastereomers were formed.



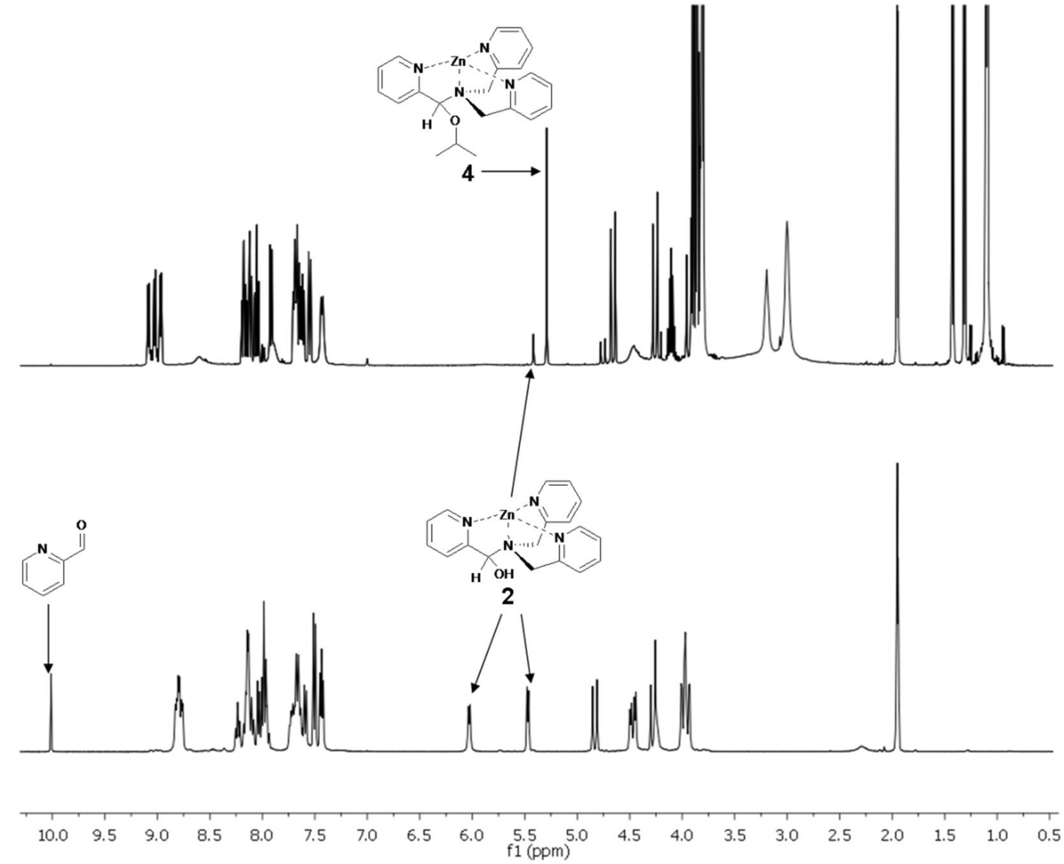
Supplementary Figure S10. ^{1}H NMR of the four-component assembly from thiazole-2-carboxaldehyde and 2-propanol with CEM-HCl (bottom panel), and after addition of **2-PA** (top panel).



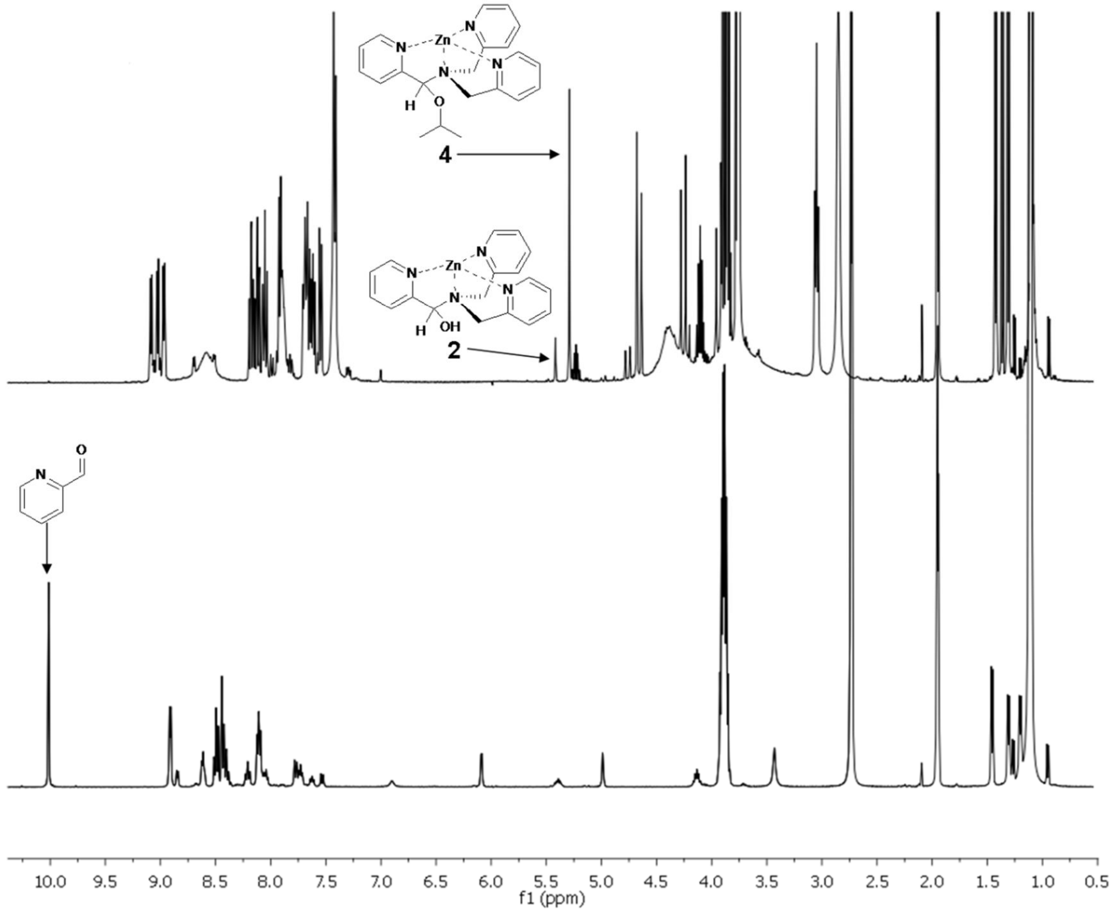
Supplementary Figure S11. ^{1}H NMR of the four-component assembly from 5-bromo-pyridine-2-carboxaldehyde and 2-propanol with CEM-HCl (bottom panel), and after addition of **2-PA** (top panel).



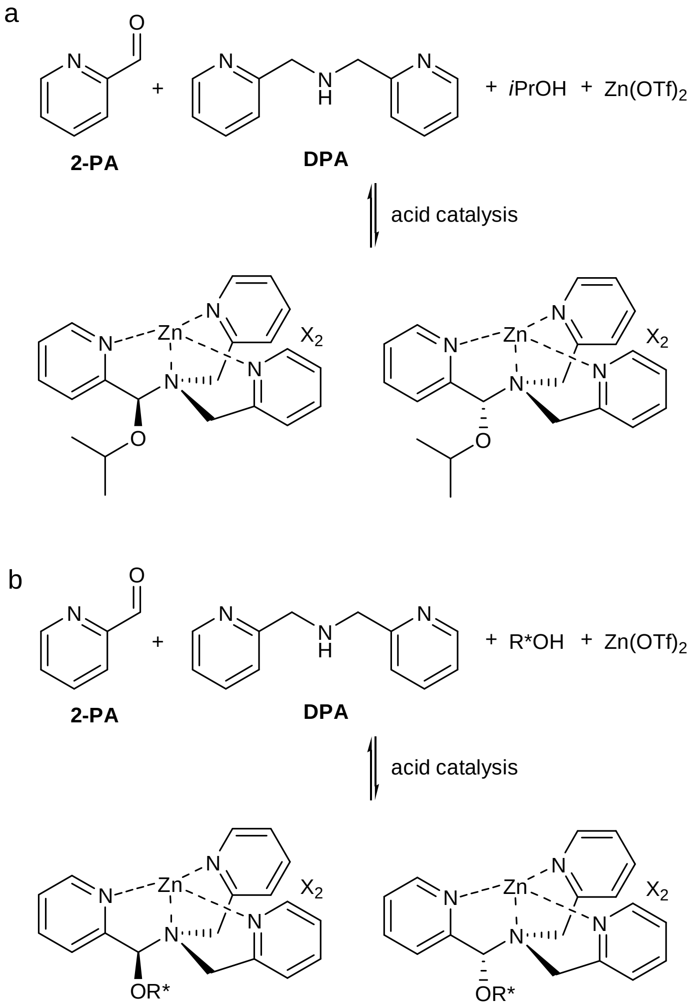
Supplementary Figure S12. ^{1}H NMR of the four-component assembly from 2-propanol with CEM-HCl in the absence of molecular sieves (bottom panel) and after addition of activated 3 Å molecular sieves (top panel). Without molecular sieves **2** increased while **4** increased with molecular sieves.



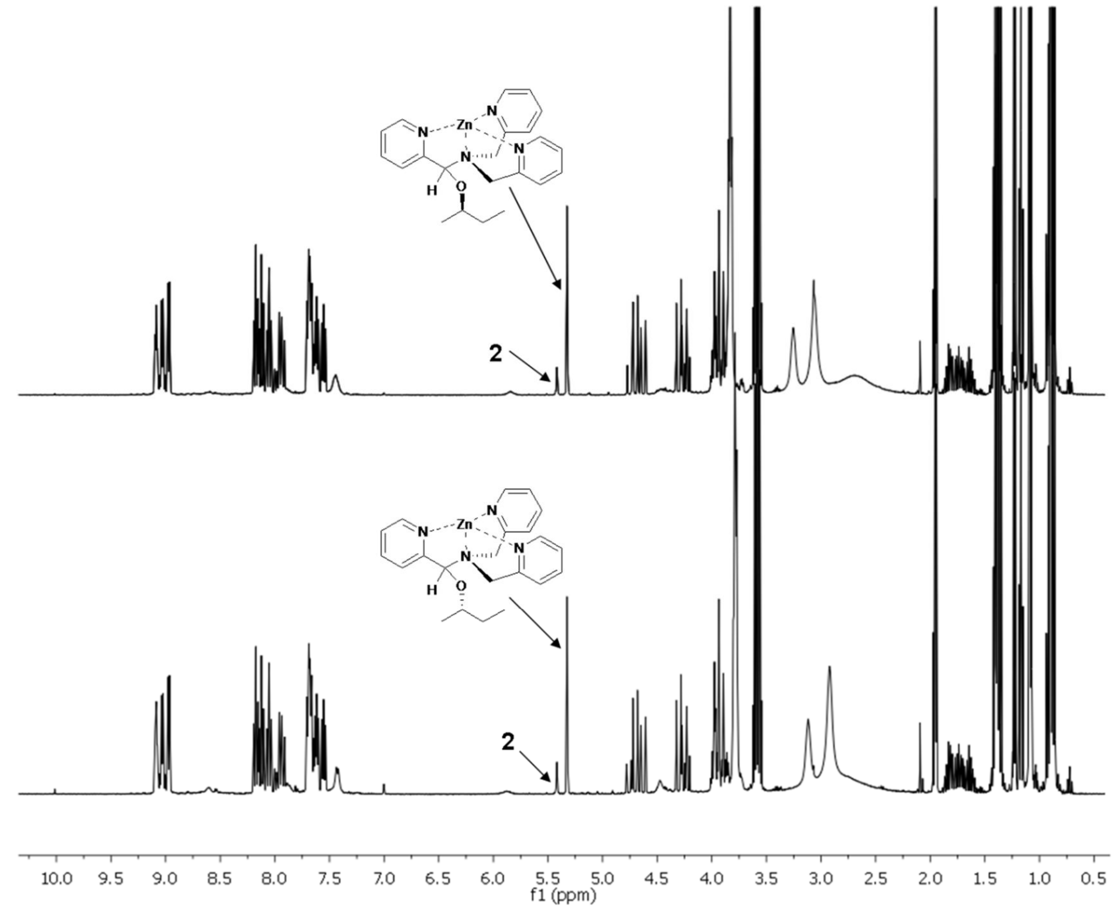
Supplementary Figure S13. The three-component assembly of **2-PA**, **DPA**, and Zn(OTf)$_2$ with molecular sieves (bottom panel), and after addition of 2-propanol and CEM-HCl (top panel).



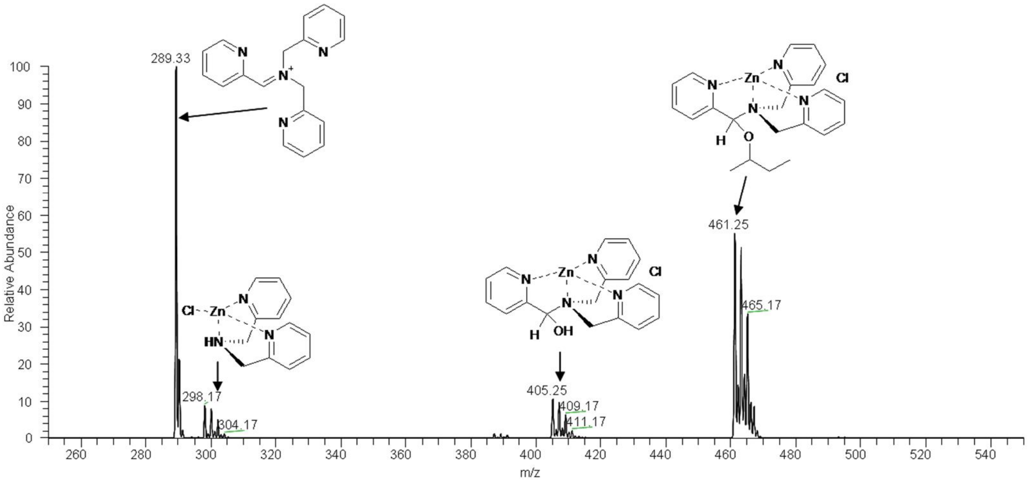
Supplementary Figure S14. The reaction of **2-PA**, Zn(OTf)$_2$ and 2-propanol with molecular sieves (bottom panel), and after addition of **DPA** and CEM-HCl (top panel).



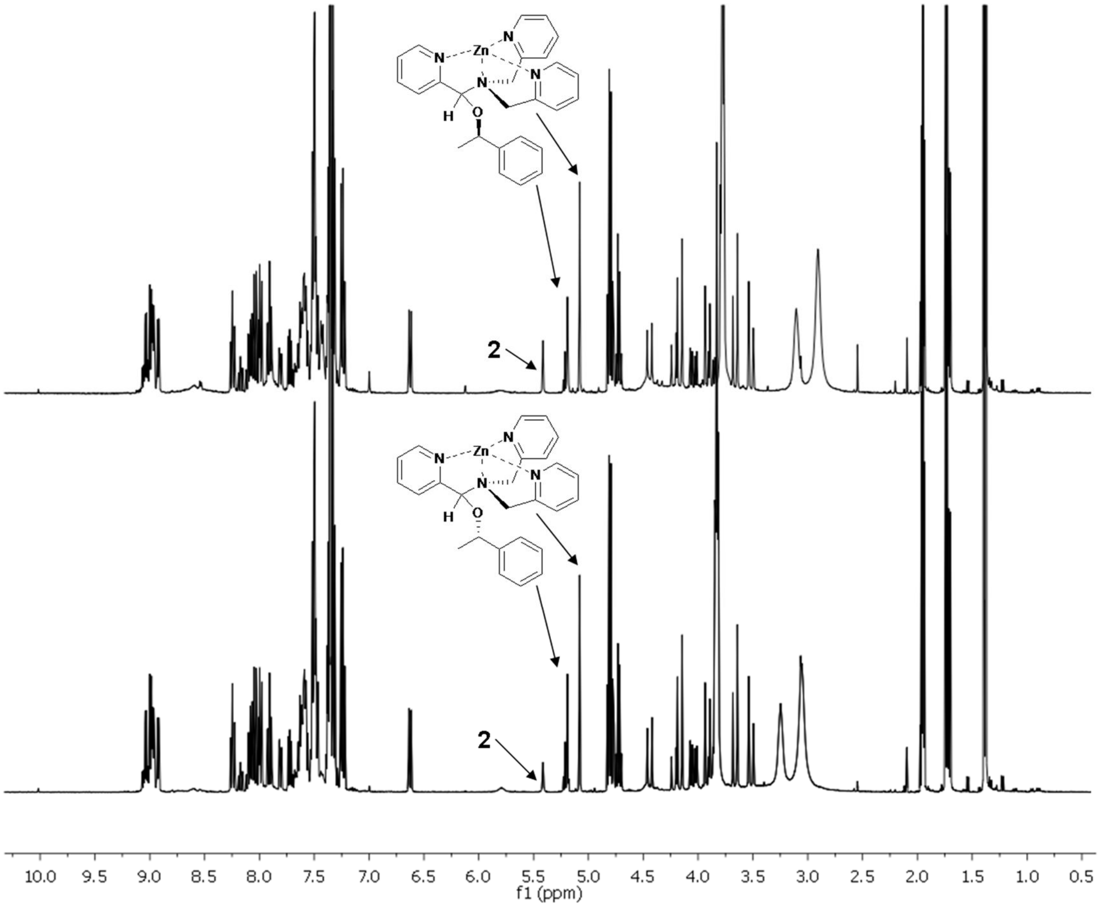
Supplementary Figure S15. a. The assembly reaction from 2-propanol creates a 1: 1 mixture of enantiomers. b. The assembly reaction from a chiral monon-ol creates diastereomers. The diastereomer ratio (*dr*) can be calculated from ^{1}H NMR integrals.



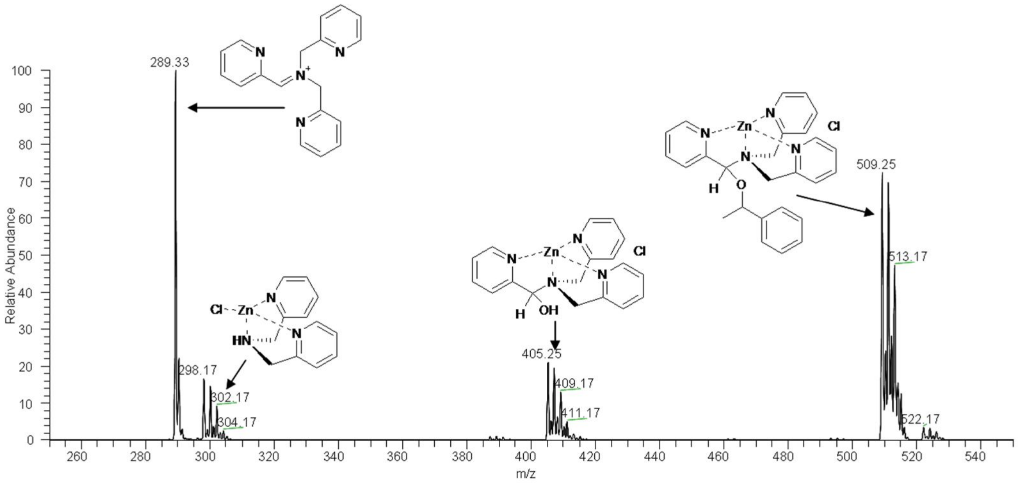
Supplementary Figure S16. ^{1}H NMR of the four-component assembly from *S*-2-butanol (bottom panel) and *R*-2-butanol (top panel) with CEM-HCl.



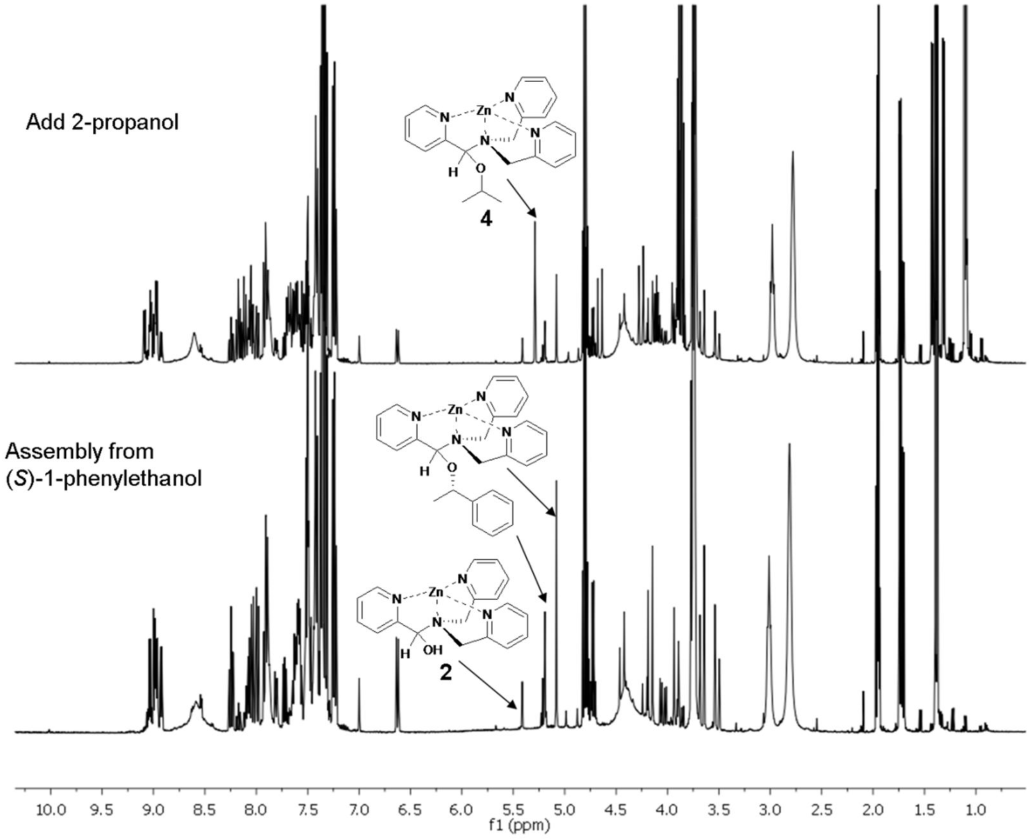
Supplementary Figure S17. ESI mass spectrum of the four-component assembly from *R*-2-butanol with CEM-HCl.



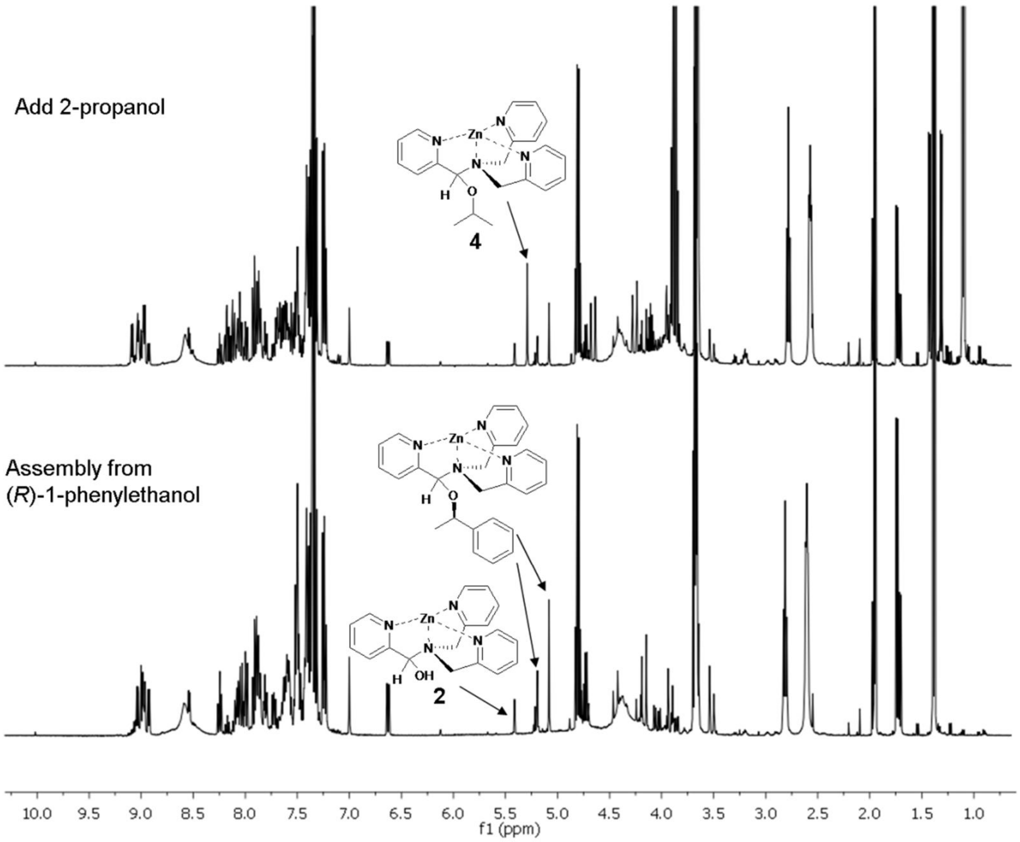
Supplementary Figure S18. ^{1}H NMR of the four-component assembly from *S*-1-phenylethanol (bottom panel) and *R*-1-phenylethanol (top panel) with CEM-HCl.



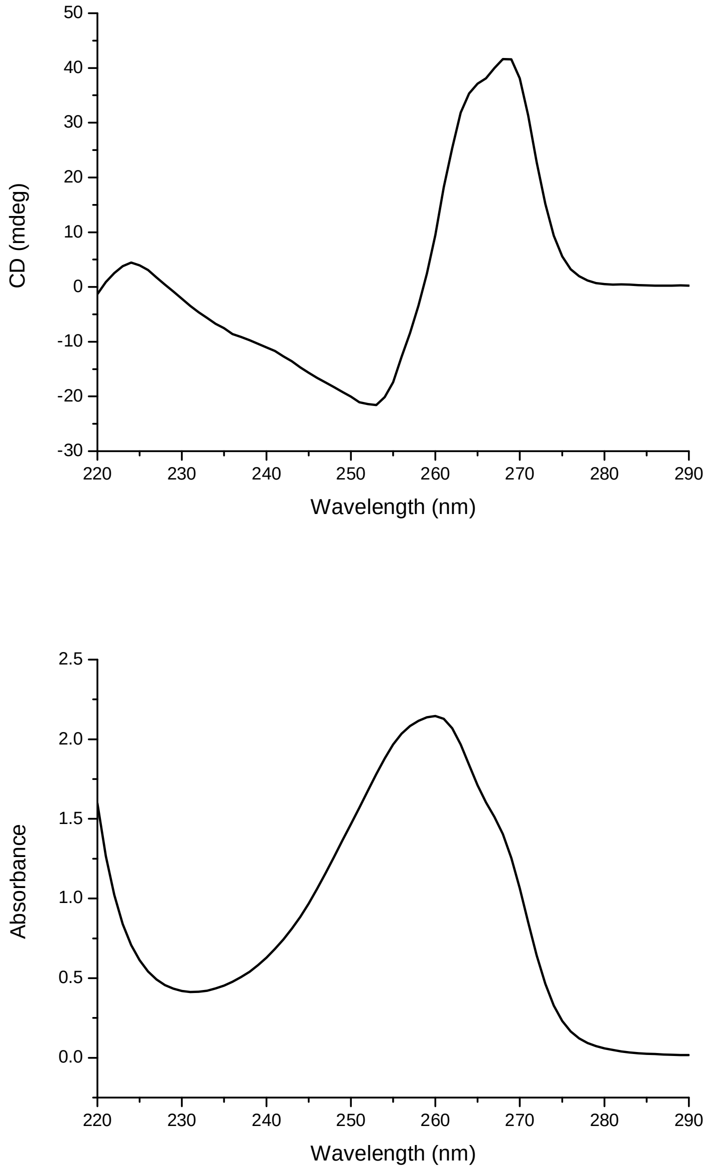
Supplementary Figure S19. ESI mass spectrum of the four-component assembly from *R*-1-phenylethanol with CEM-HCl.



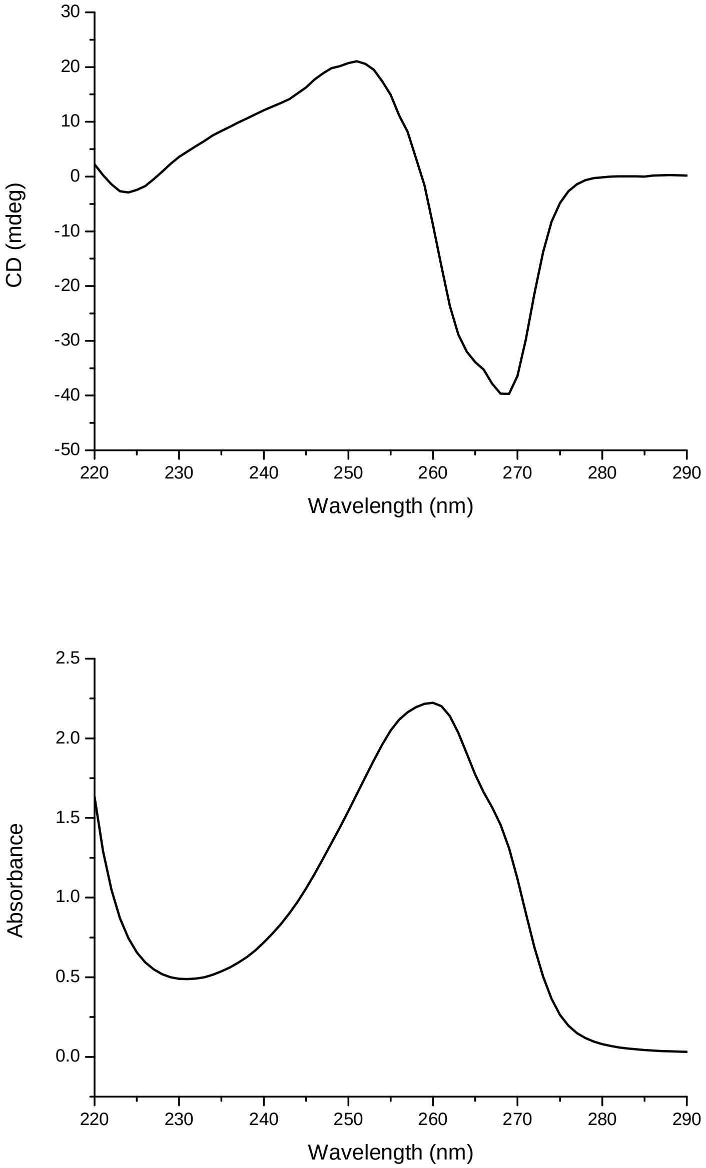
Supplementary Figure S20. ^{1}H NMR of the four-component assembly from *S*-1-phenylethanol with CEM-HCl (bottom panel), and after addition of 2-propanol (top panel).



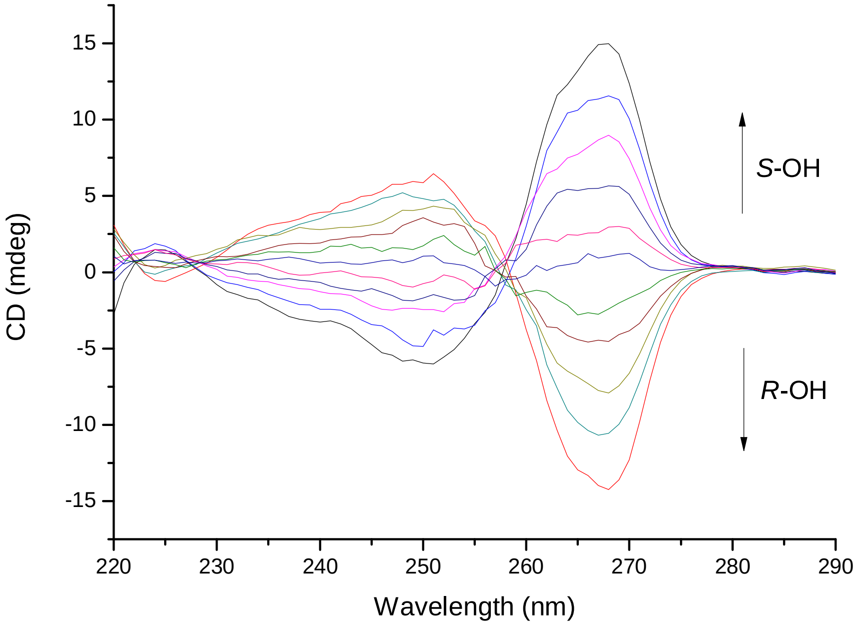
Supplementary Figure S21. ^{1}H NMR of the four-component assembly from *R*-1-phenylethanol with CEM-HCl (bottom panel), and after addition of 2-propanol (top panel).

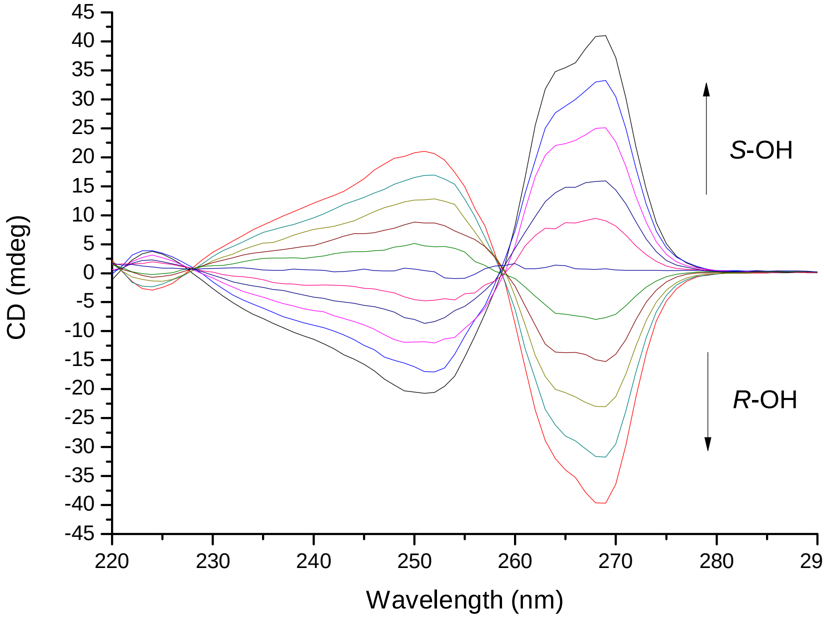


Supplementary Figure S22. CD (top panel) and UV (bottom panel) spectra of *S*-1-phenylethanol derived assembly (0.175 mM **2-PA**, 0.525 mM alcohol).

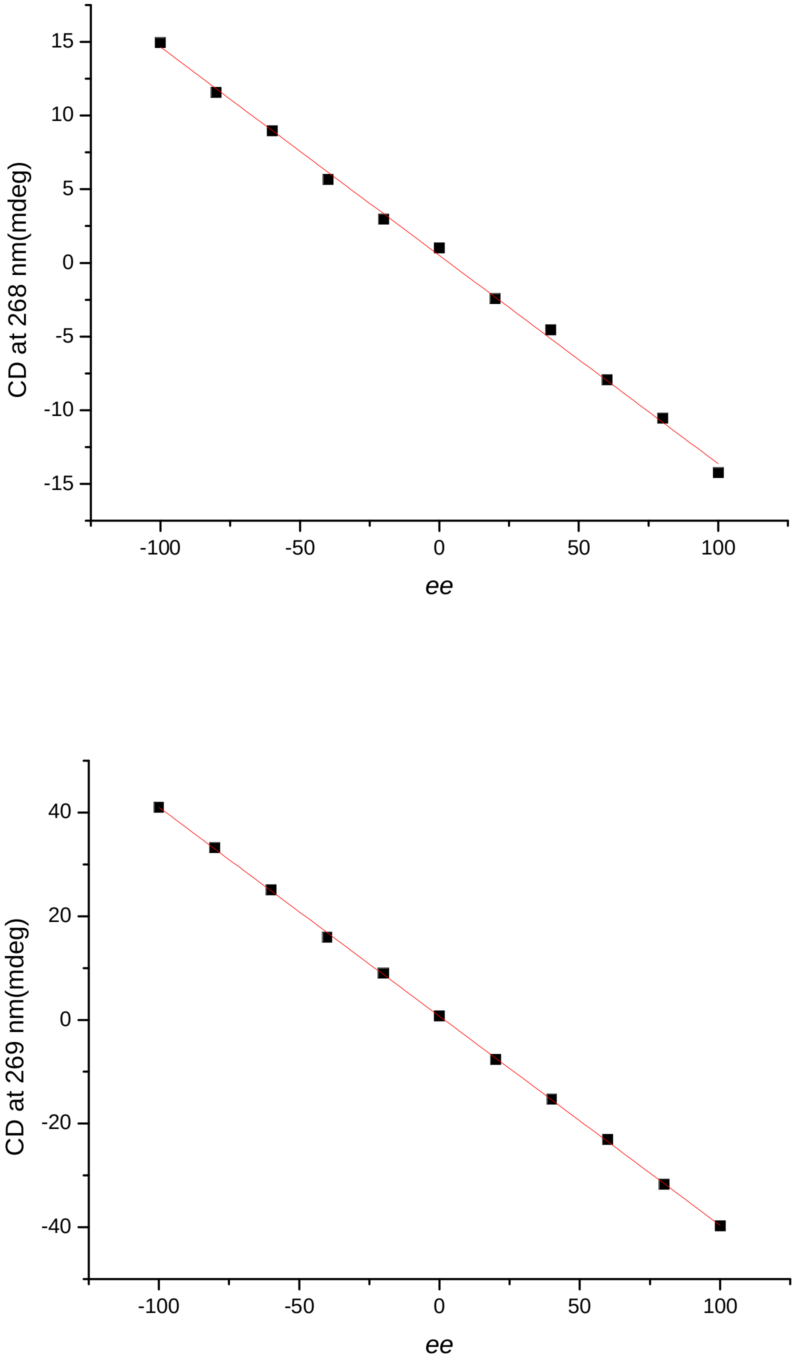


Supplementary Figure S23. CD (top panel) and UV (bottom panel) spectra of *R*-1-phenylethanol derived assembly (0.175 mM **2-PA**, 0.525 mM alcohol).

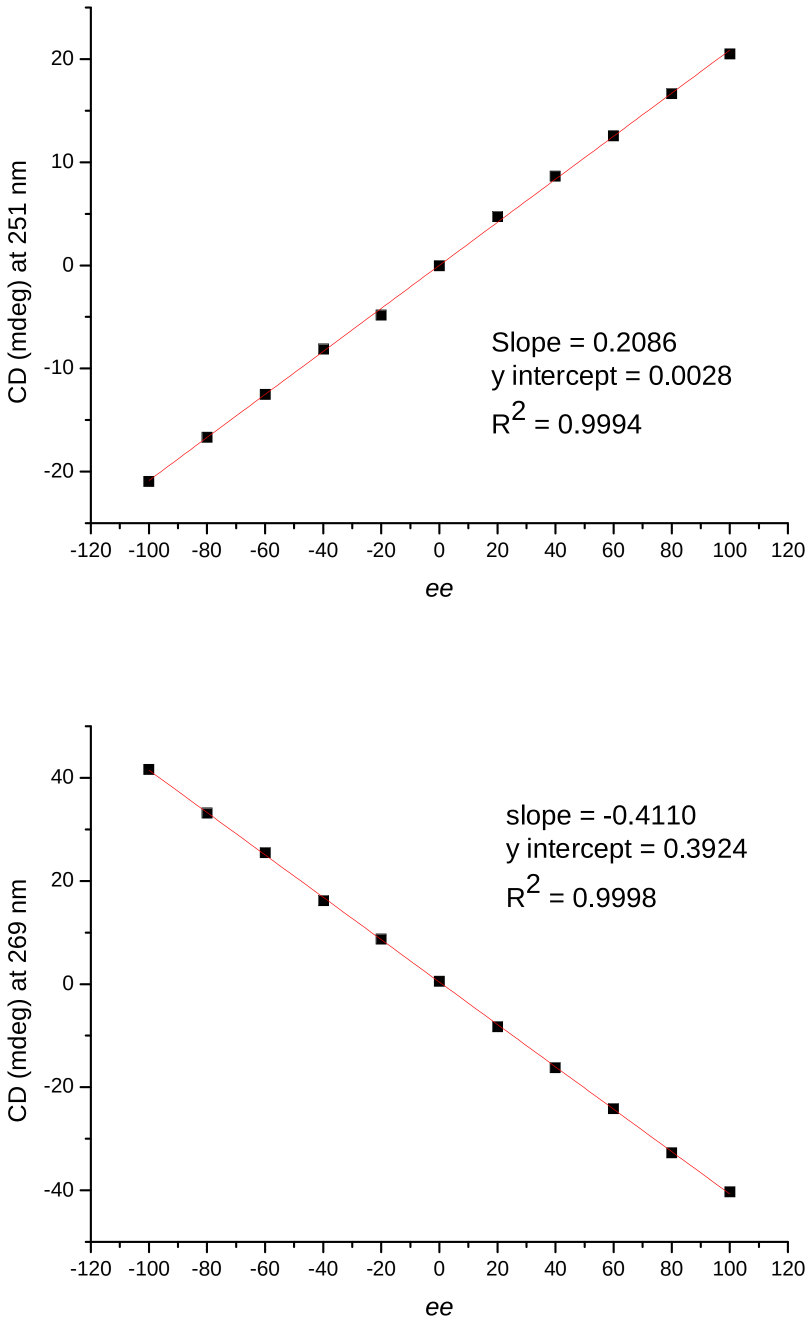




Supplementary Figure S24. CD spectra of 1-phenylethanol derived assembly (0.175 mM **2-PA**, 0.525 mM alcohol) with different *ee* without molecular sieves (top panel) and after addition of molecular sieves (bottom panel). The increase of CD signal upon addition of molecular sieves is consistent with ^{1}H NMR results.



Supplementary Figure S25. The corresponding *ee* calibration curve from Supplementary Figure S24.



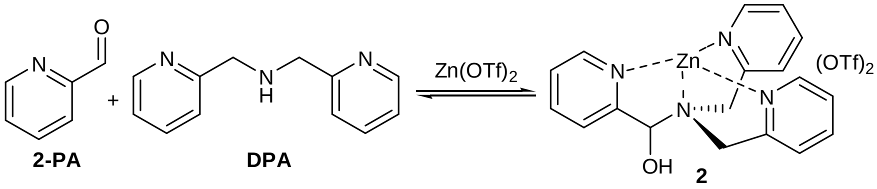
Supplementary Figure S26. The average *ee* calibration line and its linear fit at 251 nm (top panel) and 269 nm (bottom panel) for 1-phenylethanol (*see* Fig. 4d).

Supplementary Table S1. Calculated *ee* from calibration lines and the error for 1-phenylethanol.

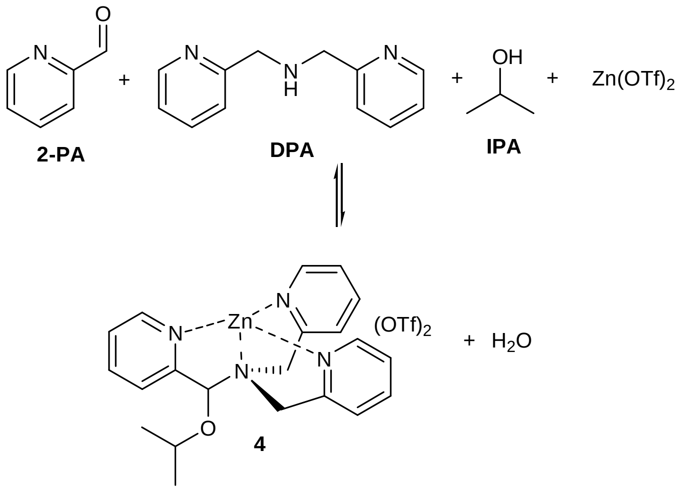
CD Data (269 nm)	Calcd. *ee*	Real *ee*	Abs. Error
38.18	-91.94	-86.67	5.27
-25.05	61.91	60.00	1.91
-27.74	68.45	73.33	4.88
14.92	-35.35	-33.33	2.02
3.97	-8.70	-6.66	2.04
-12.91	32.36	33.33	0.97
-37.13	91.30	93.33	2.03
31.53	-75.75	-73.33	2.42
9.62	-22.45	-20.00	2.45
-4.60	12.14	10.67	1.47
19.36	-46.16	-44.00	2.16
40.98	-98.76	-100.00	1.24

Equilibrium constant

For determining the equilibrium constant the assembly was conducted without molecular sieves using 2-propanol (**IPA**) as a model alcohol. An equal equivalent of **4** and water was generated assuming that the condition was dry. The Brønsted acid catalyst was not taken into consideration for the calculation of K_{eq}. In addition, we made an assumption that the non-reactive zinc was bound to the remaining **DPA** to create **Zn-DPA**, and hence, the three and four-component assemblies shown below were further simplified to two and three-component systems, respectively.



$$K(\mathbf{2}) = \frac{[\mathbf{2}]}{[\textbf{2-PA}][\textbf{Zn-DPA}]} \qquad (1)$$



$$K(\mathbf{4}) = \frac{[\mathbf{4}][\mathrm{H_2O}]}{[\mathbf{2\text{-}PA}][\mathbf{Zn\text{-}DPA}][\mathbf{IPA}]} \qquad (2)$$

Rearrange Eq. 2 with Eq. 1:

$$K(\mathbf{4}) = \frac{K(\mathbf{2})[\mathbf{4}][\mathrm{H_2O}]}{[\mathbf{2}][\mathbf{IPA}]} \qquad (3)$$

Since [**4**] = [H_2O],

$$K(\mathbf{4}) = \frac{K(\mathbf{2})[\mathbf{4}]^2}{[\mathbf{2}][\mathbf{IPA}]} \qquad (4)$$

The stability constant for **Zn-DPA**:

$$K(\mathbf{Zn\text{-}DPA}) = \frac{[\mathbf{Zn\text{-}DPA}]}{[\mathrm{Zn}][\mathbf{DPA}]} \qquad (5)$$

The equation of the equilibrium constant for the four-component assembly with **IPA**:

$$K_{eq} = \frac{[\mathbf{4}][\mathrm{H_2O}]}{[\mathbf{2\text{-}PA}][\mathrm{Zn}][\mathbf{DPA}][\mathbf{IPA}]} \qquad (6)$$

Rearrange Eq. 6 with Eqs. 2, 4, and 5:

$$K_{eq} = K(\mathbf{4})K(\mathbf{Zn\text{-}DPA}) \qquad (7)$$

$$K_{eq} = \frac{K(\mathbf{2})K(\mathbf{Zn\text{-}DPA})[\mathbf{4}]^2}{[\mathbf{2}][\mathbf{IPA}]} \qquad (8)$$

[**2**] and [**4**] can be calculated from ^{1}H NMR integrals and the mass balance of **2-PA**:

$$[\mathbf{2}] + [\mathbf{4}] + [\mathbf{2\text{-}PA}] = [\mathbf{2\text{-}PA}]_{\text{total}} \qquad (9)$$

[**IPA**] can be calculated from ^{1}H NMR integrals and the mass balance of **IPA**:

$$[\mathbf{4}] + [\mathbf{IPA}] = [\mathbf{IPA}]_{\text{total}} \qquad (10)$$

The value for K(**2**) and K(**Zn-DPA**) has been reported, and the K_{eq} of the multi-component assembly incorporating **IPA** can therefore be calculated.