Electronic Supplementary Information (ESI) for

Spontaneous mirror-symmetry breaking coupled to top-bottom chirality transfer: From porphyrin self-assembly to scalemic Diels–Alder adducts

Aitor Arlegui,[a] Bernat Soler,[a] Alex Galindo,[a] Oriol Arteaga,[b,c] Adolf Canillas, [b,c] Josep M. Ribó,[a,d] Zoubir El-Hachemi,[a,d] Joaquim Crusats[a,d,*] and Albert Moyano[a,*]

a) Department of Inorganic and Organic Chemistry, Section of Organic Chemistry; b) Department of Applied Physics; c) FEMAN Group, Institute of Nanoscience and Nanotechnology (IN2UB); d) Institute of Cosmos Science (IEEC-ICC), Universitat de Barcelona, Martí i Franquès 1, E-08028 Barcelona, Catalonia, Spain

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Materials and methods

Commercially available reagents, catalysts, and solvents were used as received with the exception of dichloromethane, which was distilled from calcium hydride under nitrogen. Water of Millipore Q quality (18.2 MW.cm, obtained from Milli-Q1 Ultrapure Water Purification Systems, Millipore, Billerica, MA) was used throughout the sample purification procedures and for the preparation of all analytical solutions of porphyrins. ^{1}H (400 MHz) NMR spectra were recorded with a Varian Mercury 400 spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS), and coupling constants (J) are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature. TMS served as an internal standard (δ = 0.00 ppm). Data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. UV-vis spectra were recorded on a double-beam Cary 500-scan spectrophotometer (Varian); cuvettes (quartz QS Suprasil, Hellma) ranging in thickness from 1 to 0.001 cm were used for measuring the absorption spectra. Circular dichroism spectra were recorded at room temperature on a JASCO J-810 spectrometer, equipped with a 150 W Xe lamp (air cooled). For the measurements, Hellma quartz Suprasil cells of different optical paths (1 mm, 0.1 mm, and 0.01 mm) were used. pH measurements were performed on a CRISON Micro pH 2000 pH-meter (Crison 52-04 glass electrode) at room temperature. The pH-meter was calibrated prior to each measurement with buffers at pH=7.00 and 4.00 (Metrohm). Reactions were monitored both by ^{1}H NMR and by thin-layer chromatography, carried out on silica gel plates Merck 60 F254, and compounds were visualized by irradiation with UV light and/or treatment with a solution of $KMnO_4$ as developing agent followed by heating. Flash column chromatography was performed using silica gel Merck 60 (particle size: 0.040 – 0.063 mm). Chiral HPLC analyses were performed with a Shimadzu LC Series 20 apparatus with an M20 diode array UV/Vis detector, using Chiralpak® IC, IA and IB columns and a Phenomenex "i-cellulose-5" LC column. The homogeneity of the peaks corresponding to the two enantiomers of the product was thoroughly checked by comparison of the UV spectra.

Synthesis and purification of the 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin-22,24-diium dihydronium salt (zw-TPPS$_4$) free of additional metal cations and counteranions (Chart ESI-1)

In a 25-mL round-bottomed flask, provided with a Dimroth condenser and a calcium chloride tube, 0.50 g (0.81 mmol) of 5,10,15,20-tetraphenylporpyrin (TPP) were slowly added to 7.0 mL of —concentrated sulfuric acid under vigorous magnetic stirring. Then, the resulting green solution was heated to 100 °C for 6 h, left to cool to room temperature, was kept under magnetic stirring for a further 24 hours, it was subsequently poured onto 25 mL of a water/ice mixture and a dark green precipitate was immediately formed. The precipitate was then transferred into a centrifuge tube and the excess of sulfuric acid was removed by repetitive centrifugation of the sediment in water at 6000 rpm during 30 minutes followed by resuspension in more water. In each cycle, the supernatant solution was carefully removed and the thick precipitate was thoroughly washed with 25 mL of water under vigorous stirring. The whole washing operation was repeated at least ten times until the pH of the supernatant solution was close to 2.0. To further eliminate any possible small molar excess of sulfuric acid without substantial loss of sample owing to partial deaggregation of the sulfonated porphyrin at higher pH values of the supernatant solution —note that in the absence of sulfuric acid, the pH of the medium is regulated by zw-TPPS4 which protonated pyrroleninic nitrogen atoms show a pKa value of ~5.0[1] and that its conjugated base does not form self-assembled supramolecular structures— additional resuspensions of the remaining sediment were performed twice with 25 mL of a 0.1 M aqueous solution of HCl, and the sediment was finally washed twice again with water. The obtained dark-green precipitate was lyophilized and 0.55 g (0.57 mmol, 70% yield) of the title compound were obtained as a dark-green solid whose characterization data was in full agreement with that previously reported.[1]

For all synthetic batches of zw-TPPS$_4$ a spectrophotometric titration with isoindoline was performed so as to be sure that the final compound was free of any traces of sulfuric acid. The titration process could be conveniently followed by UV-vis spectroscopy using the absorptions bands of the free-base TPPS$_4$ and those of its diprotonated counterpart (initially aggregated, and after the addition of the first two equivalents of isoindoline in its monomeric form). As expected, a complete neutralization of the sample was obtained just after the addition of four equivalents of the secondary amine (zw-TPPS$_4$ behaving as a tetrasulfonic acid), indicating that the washing procedure described above was successful. The titration was performed at relatively high concentrations of porhyrin (*ca* 10^{-4} M using 0.1 mm cells) to avoid its deprotonation by dilution (inner protons of the porphyrin ring, pKa ~ 5.0); higher concentrations of the porphyrin proved to be ineffective for the titration process owing to the presence of kinetic effects originating from the

stability of the aggregates. The stoichiometric 1:2 complex with isoindoline was then simply prepared using the appropriate amounts of starting materials.

The regioisomeric purity of the zw-TPPS$_4$ (Chart ESI-1) samples obtained was assessed by reverse-phase analytical HPLC. The HPLC analyses were performed on a Shimadzu high-performance liquid chromatograph equipped with two LC-10AS pumps, a Shimadzu CBM controller, an analytical precolumn Resolve C18 (Waters), and a Nucleosil 120-5C18 analytical column, using an elution gradient consisting of a mixture of methanol and tetrabutylammonium phosphate buffer (3 mmol·L^{-1}; pH=7.0) (1:1 v:v) to pure methanol over a period of 30 minutes at a flow rate of 0.6 mL min^{-1} (~2700 - 1050 psi). All solvents were of HPLC grade and were carefully degassed prior to use. At time 0 the sample was injected. The elution profile was monitored at λ = 414 nm (UV-Vis detector SPD-6AV). A representative chromatogram is shown in Figure ESI-1. Variable amounts of the regioisomer corresponding to a porphyrin in which one of the sulfonato groups is located in a *meta* position of a *meso*-phenyl ring were always detected.[2] Note, though, that the metal-cation-and-counteranion-free nature of the title porphyrin precludes the synthesis of isomerically pure samples in large enough quantities for the organocatalysis experiments via semipreparative reverse-phase HPLC purification or regioselective synthesis,[2] followed by ion exchange chromatography. Thus, all synthetic experiments reported in this communication were performed with zw-TPPS$_4$ samples of a regioisomeric purity similar to that presented in Fig. S1.

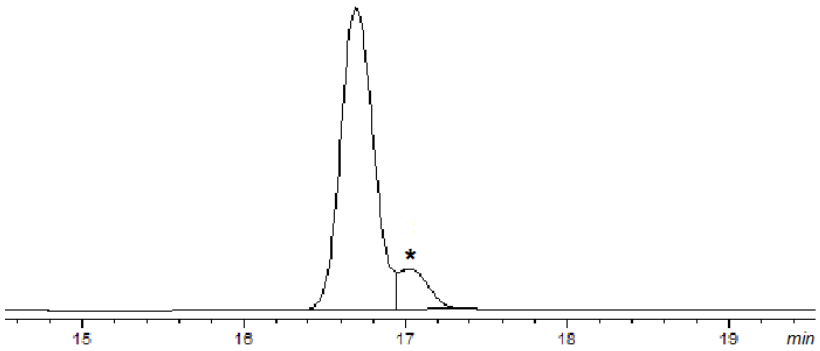


Figure ESI-1. Reverse-phase analytical HPLC chromatogram of a typical zw-TPPS$_4$ sample obtained as described above. *Impurity, up to a 15% of the total amount of the sample depending on the batch of sulfonation; the characterization of this compound as 5-(3-sulfonatophenyl)-10,15,20-tris(4-sulfonatophenyl)porphyrin was reported in ref.[2] Under the experimental conditions of sulfonation reported above, partially sulfonated porphyrins bearing three or less sulfonato groups were not detected in any case.

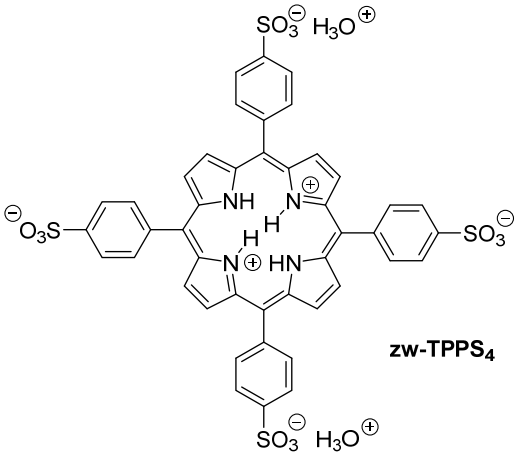


Chart ESI-1

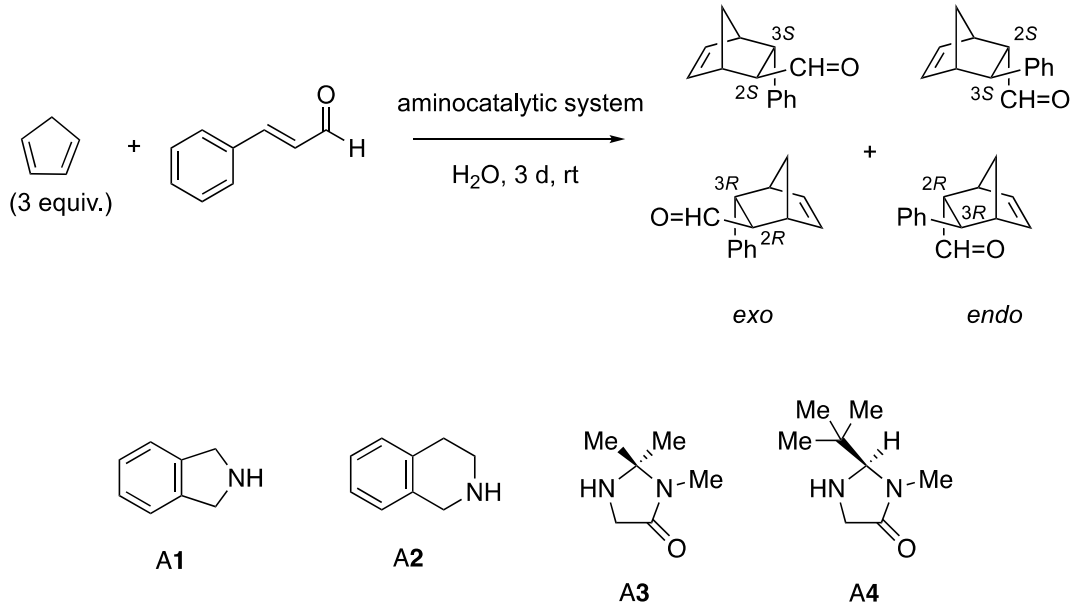
Selection of a specific supramolecular chiral sign in the formation of the 1:2 heteroaggregate between zw-TPPS$_4$ and isoindoline [zw-TPPS$_4$·(isoindoline)$_2$]

A new dilution and reconcentration method in the presence of traces of a molecule acting as a chiral selector, which is compatible with the particular characteristics of zw-TPPS$_4$ samples, was adapted from ref[3]. All manipulation of diluted aqueous solutions of zw-TPPS$_4$ (green color) were performed using low-density polyethylene (LDPE) plastic laboratory material (e.g. micropipetes: Brand AG) owing to the prompt neutralization of the sample leading to the free-base porphyrin (red color) when in contact with borosilicate or normal glass pipettes and glassware. Previous treatment of the Pyrex borosilicate glass with hydrochloric acid delayed the neutralization, and the trimethoxy silanization of the glass fully avoided the phenomenon. Thus, in order to overcome this problem, all of the aqueous solutions of zw-TPPS$_4$ were used freshly prepared and manipulated in glassware which had been previously treated with a 20% NaOH aqueous solution for 30 minutes, dried, rinsed with ethanol, dried again, and finally treated with a 1:4 mixture of $(CH_3)_3SiCl : CH_2Cl_2$ for another 30 minutes.

In a 1 L round-bottomed flask, previously silanized as described above, 75 mg (0.076 mmol) of zw-TPPS$_4$ were gradually diluted with a 5:1 mixture of water and methanol until zw-TPPS$_4$ was only present in the solution in its achiral monomeric form (approximately 500 mL; checked by UV-vis spectroscopy in a cell with a path of 0.5 cm through the disappearance of the absorption band at 489 nm corresponding to the aggregated form of the porphyrin; thiner cells induced the aggregation of the porphyrin and could not be used to assess its aggregation state in the original sample). Then, 3.5 mg (0.0077 mmol) of (*R*) or (*S*)-*N*,*N*-dimethyl-*N*-(1-phenylethyl)hexadecan-1-aminium bromide [(*R*)-Q, (*S*)-Q] were added into the solution of monomeric porphyrin and the resulting mixture was slowly concentrated at the rotary evaporator to a final volume of ~3 mL, 17 μL of isoindoline (0.15 mmol) were added, and the resulting solution was used for the experiments of organocatalysis. The supramolecular chirality sign of the homoassociated form of zw-TPPS$_4$ was conveniently monitored by CD spectroscopy throughout the aggregation process before the final concentration was reached, using cells of different path lengths depending on the concentration of the sample.

Optimization of the aminocatalytic conditions for the aqueous Diels–Alder reaction

We selected for our study the Diels-Alder cycloaddition between (*E*)-cinnamaldehyde and cyclopentadiene (Scheme ESI-1), as a prototypical Brønsted acid- or iminium-promoted aqueous reaction that can be run in the absence of any organic co-solvent.



Scheme ESI-1. Aqueous Diels-Alder reaction between cyclopentadiene and (*E*)-cinnamaldehyde, and cyclic secondary amines used as co-catalysts.

We examined in the first place the catalytic efficiency of the *p*-toluenesulfonate salts of some of the achiral (A**1**, A**2**, A**3**) or chiral racemic (A**4**) amines that we planned to use in conjunction with the zw-TPPS$_4$ J-aggregates in our chirality transfer experiments (Table ESI-1, entries 1-4). The highest conversion (75% after 3 days at rt) was obtained with a 30 mol% of isoindoline (A**1**) *p*-toluenesulfonate (entry 1), and in the same conditions tetrahydroisoquinoline A**2** was much less efficient (entry 2 in Table 1); MacMillan's imidazolidinones A**3** and A**4** (racemic) gave 50% conversion after three days (entries 3 and 4, respectively). When the isoindoline amount was reduced to a 15 mol%, the conversion was much lower (less than 10% after 3 days). Taking into account the acceleration of Diels-Alder reactions both "in water"[4] and "on water"[5] conditions, we performed the reaction in the absence of any catalyst, and we found a maximum 2% conversion after 3 days at rt (entry 5 in Table ESI-1). With these data in hand, we selected isoindoline as the benchmark aminocatalyst in our experiments.

Table ESI-1. Aqueous Diels-Alder reaction between cyclopentadiene and (*E*)-cinnamaldehyde, under catalysis by amine-*p*-toluenesulfonates (Scheme 1).[a]

Entry	Acid	Amine[b]	Conversion (%) [c]	*exo*:*endo* ratio [c]
1	*p*-TsOH	A**1**	75	70:30
2	*p*-TsOH	A**2**	25	55:45
3	*p*-TsOH	A**3**	50	57:43
4	*p*-TsOH	A**4**	50	70:30
5	–	–	<2	52:48

[a] The reaction was conducted by using (*E*)-cinnamaldehyde (0.50 mmol), cyclopentadiene (1.5 mmol), amine (0.15 mmol) and *p*-TsOH (0.15 mmol) under stirring at room temperature for 3 days in water (2 mL). [b] A**1** = isoindoline; A**2** = 1,2,3,4-tetrahydroisoquinoline; A**3** = 2,2,3-trimethylimidazolidin-4-one; A**4** = *rac*-2-(*tert*-butyl)-3-methylimidazolidin-4-one (Scheme ESI-1). [c] Conversion and *exo*:*endo* diastereomer ratio were determined from the integration of the aldehyde proton signals in the 400 MHz ^{1}H-NMR spectra of the reaction crudes.

^{1}H-NMR signals used to determine the conversion and the diastereoselectivity of the organocalyzed Diels-Alder reaction

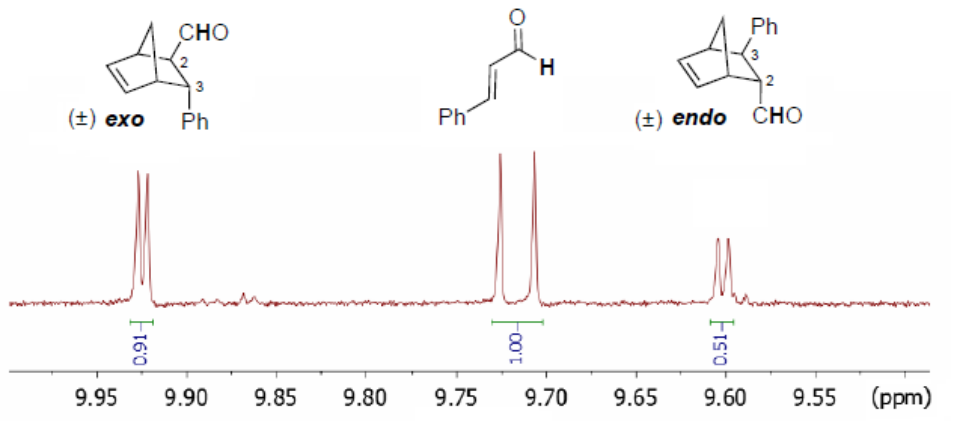


Figure ESI-2. Region of the ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) corresponding to the aldehyde proton signals used to determine the conversion and the diastereoselectivity of the organocalyzed Diels-Alder reaction.

Catalysis of the aqueous Diels–Alder reaction by isoindolinium salts

The reaction was performed at room temperature in a non-stoppered 10 mL round-bottomed flask. Freshly distilled (*E*)-cinnamaldehyde (66 mg, 63 μL, 0.50 mmol) was added to a magnetically stirred, homogeneous solution of isoindoline (18 mg, 0.15 mmol) to an aqueous 0.1 M AcOH/NaOAc buffer solution (2 mL, pH 6.7 or 3.6). After stirring for 2 min, freshly distilled cyclopentadiene (1.5 mmol, 117 μL) was added in one portion. After 72 h, the resulting suspension was extracted with dichloromethane (3x10 mL) and then the organic solution was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to leave the crude product, which was purified by column chromatography on silicagel (eluting with a 15:1 hexanes/ethyl acetate mixture) to furnish a mixture of the racemic *endo*-(1*RS*,2*SR*) and the *exo*-(1*RS*,2*RS*) Diels–Alder adducts. The *endo*/*exo* ratio was determined from the ^{1}H NMR spectrum of the crude material. In an alternative experimental procedure, (*E*)-cinnamaldehyde (0.50 mmol) and cyclopentadiene (1.5 mmol) were sequentially added to the homogeneous solution obtained from isoindoline (18 mg, 0.15 mmol) and *p*-toluenesulfonic acid monohydrate (28 mg, 0.15 mmol) in water (2 mL).

Catalysis of the aqueous Diels–Alder reaction by the [zw-TPPS$_4$·(amine)$_2$] heteroaggreates without the use of any chiral selector

As described above, in order to obtain the chiral porphyrin aggregates in acidic aqueous media without the need of acidification (so as not to add additional achiral counteranions that could compete with the ACDC approach) we prepared the 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin-22,24-diium dihydronium salt (zw-TPPS$_4$) form of the porphyrin by direct sulfonation of 5,10,15,20-tetraphenylporphyrin (TPP), followed by purification of the aggregated zwitterionic form without any neutralization process involved in the work-up procedure. Then, simply by addition of two molar equivalents of the corresponding secondary amine (Scheme ESI-1) used as co-catalyst to a solution of zw-TPPS$_4$, the ionic chiral [TPPS$_4$·(amine)$_2$] heteroaggregates used as catalysts were straightforwardly obtained. Some of he results obtained in these preliminary experiments are summarized in Table ESI-2.

First, we set out to test the effect of zw-TPPS$_4$ J-aggregate alone in the Diels-Alder cycloaddition. In two independent experiments (entries 1 and 2 in Table ESI-2), we found a small but measurable acceleration effect (*ca.* 7% conversion after 3 days *vs.* less than 2% in the absence of any acidic catalyst, entry 5 in Table ESI-1). Contrary to the amine *p*-toluenesulfonate-catalyzed reactions of

entries 1-4 in Table ESI-1, we found a small preference for the *endo*-diastereomer (*ca.* 40:60 *exo*:*endo* dr), and most importantly, we could observe that both diastereomers were obtained in scalemic form, albeit with very low enantiomeric purity.

Table ESI-2. Selected results for the aqueous Diels-Alder reaction between cyclopentadiene and (*E*)-cinnamaldehyde, under catalysis by zw-$TPPS_4$ aggregates or by zw-$TPPS_4$·(amine)$_2$ heteroaggregates.[a]

Entry	Acid	Amine[b]	Conversion (%) [c]	*exo*:*endo* [c]	Ee(*exo*) ± 0.6%[d] (configuration)[e]	Ee(*endo*) ± 0.6% [d] (configuration)[e]
1	zw-$TPPS_4$	–	7.3	42:58	2.7 (2*R*,3*R*)	1.0 (2*S*,3*S*)
2	zw-$TPPS_4$	–	7.0	42:58	3.0 (2*R*,3*R*)	1.3 (2*R*,3*R*)
3	$TPPS_4$/NaCl [f]	–	14	43:57	1.4 (2*R*,3*R*)	0.4 (2*S*,3*S*)
4	$TPPS_4$/NaCl [f]	–	13	40:60	4.4 (2*R*,3*R*)	0.7 (2*S*,3*S*)
5	zw-$TPPS_4$	A**1**	22	57:43	2.3 (2*R*,3*R*)	2.3 (2*S*,3*S*)
6	$TPPS_4$/NaCl [f]	A**1**	37	57:43	1.2 (2*S*,3*S*)	2.4 (2*S*,3*S*)
7	zw-$TPPS_4$	A**2**	10	50:50	3.4 (2*R*,3*R*)	1.3 (2*R*,3*R*)
8	zw-$TPPS_4$	A**2**	4	52:48	1.4 (2*S*,3*S*)	2.8 (2*S*,3*S*)
9	zw-$TPPS_4$	A**3**	29	55:45	3.9 (2*S*,3*S*)	5.9 (2*R*,3*R*)
10	zw-$TPPS_4$	A**4**	33	71:29	2.8 (2*R*,3*R*)	0.4 (2*S*,3*S*)

[a] Unless otherwise indicated, the reaction was conducted by using (*E*)-cinnamaldehyde (0.50 mmol), cyclopentadiene (1.5 mmol), amine (0.15 mmol) and/or zw-$TPPS_4$ (0.075 mmol) under stirring at room temperature for 3 days in water (2 mL). It should be noted that owing to the stochastic nature of the supramolecular aggregation process of the zw-$TPPS_4$ porphyrin, somewhat different results were obtained for each individual reaction, independently of the synthetic batch of zw-$TPPS_4$. [b] A**1** = isoindoline; A**2** = 1,2,3,4-tetrahydroisoquinoline; A**3** = 2,2,3-trimethylimidazolidin-4-one; A**4** = *rac*-2-(*tert*-butyl)-3-methylimidazolidin-4-one (Scheme ESI-1). [c] Conversion and *exo*:*endo* diastereomer ratio were determined from the integration of the aldehyde proton signals in the 400 MHz ^{1}H-NMR spectra of the reaction crudes. [d] Determined by HPLC on a chiral stationary phase, after reduction of the aldehyde adduct mixture to the corresponding alcohols ($NaBH_4$/MeOH). [e] Absolute configuration, see reference [6]. [f] The acidic form of $TPPS_4$ (protonation of the pyrroleninic nitrogen atoms) was generated *in situ* by treating the tetrasodium salt of $TPPS_4$ (0.075 mmol) with conc. HCl (0.15/0.30 mmol).

When the reactions were run in the presence of NaCl (30 mol% in entry 3, 60 mol% in entry 4), a positive "salting out" effect on the reaction yield (from 7% to 14%) was revealed, consistent with the presence of stabilizing hydrophobic interactions in the transition state.[4b] The ee's of the *exo* diastereomers in entries 1-4 are higher than those of the corresponding *endo* isomers. These experiments gave support to our idea that zw-$TPPS_4$ J-aggregates could be regarded as chiral,

heterogeneous supramolecular sulfonic acids, and our next step was that of examining the possibility of a more efficient chirality transfer in an ACDC-type scenario, in which the zw-$TPPS_4$ J-aggregate would provide the chiral counteranion of the α,β-unsaturated iminium ion generated from cinnamaldehyde and the [$TPPS_4$·(amine)$_2$] heteroaggregate.

We performed next the Diels-Alder reaction in the presence of a 15 mol% of the [$TPPS_4$·(isoindoline)$_2$] heteroaggregates prepared "in situ" by the addition of 2 molar equivalents of isoindoline A**1** to a stirred suspension of the zw-$TPPS_4$ homoaggregate in water. In several independent experiments, the yield of the Diels-Alder adduct mixture ranged from 22 to 43%, and they were clearly higher than those obtained using zw-$TPPS_4$ alone. In these conditions, a slight preference for the formation of the *exo* adduct was observed (*ca*. 57:43 *exo*:*endo* dr). In one experiment (entry 5 in Table ESI-2) both diastereomers were obtained with similar enantiomeric purity. When the $TPPS_4$ J-aggregates were prepared by adding a controlled amount of HCl to a solution of the tetrasodium salt of $TPPS_4$, so that NaCl was present in the reaction medium (entry 6 in Table ESI-2), the positive "salting out" effect on the reaction yield was again observed, although no significant changes were apparent in the enantiomeric excesses of the adducts. This could be explained by assuming that, even in the presence of chloride anions in the medium, the iminium intermediate remains in the proximity of the sulfonate anions at the J-aggregate surface. The catalytic efficiency of the tetrahydroisoquinoline-derived [$TPPS_4$·(A**2**)$_2$] heteroaggregate (entries 7 and 8 in Table ESI-2) was, as expected from the comparative performances of A**1** and A**2** in entries 1 and 2 in Table ESI-1, much lower than that of the [$TPPS_4$·(A**1**)$_2$] heteroaggregate; on the other hand, it is worth noting that in two independent experiments both the *exo*- and the *endo*-Diels-Alder adducts were clearly obtained in nonracemic form (1.3-3.4% ee). Interesting results were obtained with the achiral imidazolidinone A**3**: in the experiment summarized in entry 9 in Table ESI-2, that took place with a conversion of 29%, the *endo*-(2*R*,3*R*) adduct was obtained with a 5.9% ee, (3.9% ee for the *exo*-(2*S*,3*S*) adduct). Similar conversions were obtained when the chiral, racemic imidazolidinone A**4** was used to prepare the heteroaggregate (see entry 10 in Table ESI-2).

In summary, optically active products (%ee > 0.5% for at least one of the two diastereomeric Diels-Alder adducts) were obtained in most of the experiments performed in the presence of the $TPPS_4$-based aggregates. Regarding the sense of the chiral induction in these catalysed reactions, the distribution of the absolute configuration of the major enantiomers of the adducts showed a significant bias from the stochastic one, and that there appears to be (taking into account only the samples with an %ee higher than 0.8) a preference of *ca.* 2:1 for the (2*R*,3*R*)-*exo*/(2S,3S)-*endo* pairs over other combinations. Nevertheless, in these reaction conditions, a correlation of the ee's of the

Diels-Alder adducts with the supramolecular chirality of the J-heteroaggregates is not possible, for several reasons:

a) Conventional CD measurements cannot be performed at the final concentrations needed for the catalysis experiments, due to the inhomogeneous character of the samples.

b) In the high zw-$TPPS_4$ concentrations needed for the organocatalyzed Diels-Alder reactions (ca. $4x10^{-2}$ M) the chiral outcome of the porphyrin SMSB self-assembling process is known to be unavoidably biased always to the same chiral sign (see ref. 22 in the main text).

Taking this into account, we decided to perform the experiments based on the chiral selectors, summarized in Table 1 in the main text. A correlation of the ee's of the Diels-Alder adducts with the supramolecular chirality of the J-heteroaggregates was not possible otherwise; we think that the results summarized above and obtained in the absence of selectors, may not be conclusive unless the required correlation between mirrored conditions is accomplished. Only when the chirality sign selection process could be successfully developed, and experimental mirrored conditions were achieved, a correlation between chiralities at different length-scales could be established and, in this way, a false conclusion derived from any potential experimental artifact (e.g. due to traces of unavoidable contaminants in the HPLC analysis) was ruled out.

Catalysis of the aqueous Diels–Alder reaction by the [zw-$TPPS_4$·(isoindoline)$_2$] heteroaggreates of a chosen chiral sign

In a typical experiment presented in Table 1 of the main text, a suspension of the supramolecular [zw-$TPPS_4$·(isoindoline)$_2$] catalyst of a chosen chiral sign was prepared as described above. Then, freshly distilled (*E*)-cinnamaldehyde (66 mg, 63 μL, 0.50 mmol) and freshly distilled cyclopentadiene (126 μL, 1.50 mmol) were sequentially added to the aqueous suspension of the catalyst, and the resulting heterogenous mixture was left to react under magnetic stirring of the resulting slurry. After 72 hours, the reaction crude was poured onto water (7 mL), and the mixture was extracted with dichloromethane (4 x 10 mL). The combined organic phases were thoroughly washed with a saturated $NaHCO_3$ solution (2 x 15 mL). Finally, the solution was dried over Na_2SO_4 and the organic solvent was eliminated under reduced pressure affording the crude mixture of Diels–Alder adducts (see Scheme 2 in the main text) as a dark-yellow oil. In order to determine the conversion of the reaction and the diastereomeric ratio of the products, this crude mixture was analysed by ^{1}H-NMR.

The enantiomeric excesses were determined as follows: The Diels–Alder reaction crude was purified by column chromatography using a 15:1 hexane/AcOEt mixture as eluent, furnishing a chromatographically homogeneous pale-yellow oil (one spot by TLC, 2:1 hexane/AcOEt, Rf = 0.63). Then, in a 10 mL round-bottomed flask, sodium borohydride (152 mg, 4.0 mmol) was added to a solution of the mixture of Diels–Alder adducts (22 mg, 0.11 mmol) in methanol (2 mL) under vigorous stirring. After 24 hours at room temperature, the reaction crude was poured onto water (10 mL), the aqueous layer was washed with dichloromethane (4 x 10 mL) and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (2 x 15 ml), and finally dried over Na_2SO_4. The organic solvent was eliminated under reduced pressure affording the crude product. Chromatographic purification on silica gel, eluting with a 3:1 hexane/AcOEt mixture, furnished a chromatographically homogeneous (2:1 AcOEt : C_6H_{14}, R_f = 0,36) light yellow oil (18 mg, 82% yield) that was submitted to chiral HPLC analysis.

Conditions for the HPLC analysis: Phenomenex® I-Cellulose-5 column, 99.2:0.8 hexane/2-propanol, 1 mL/min, 25ºC, λ = 210 nm. t_R (*exo*-1*R*,2*R*,3*R*,4*S*) = 34.2 min, t_R (*endo*-1*S*,2*R*,3*R*,4*R*) = 41.4 min, t_R (*exo*-1*S*,2*S*,3*S*,4*R*) = 43.8 min, t_R (*endo*-1*R*,2*S*,3*S*,4*S*) = 46.8 min. The retention times for each stereoisomer were unambiguously assigned by comparison with the HPLC trace of the alcohol mixture resulting from reduction of the Diels–Alder adducts obtained by catalysis of the reaction by the $HClO_4$ salt of (*S*)-bis(3,5-trifluoromethylphenyl)prolinol trimethylsilyl ether (5 mol%, water, rt, 7 h), according to Hayashi and co-workers.[6]

CD spectra of $TPPS_4$ samples at high concentrations without the use of any chiral selector

The Spontaneous Mirror Symmetry Breaking (SMSB) during the aggregation process of $TPPS_4$ in acidified aqueous media has been previously established by Mueller Matrix (MM) polarimetry.[7] In order to follow the Asymmetric Counteranion Directed Catalysis (ACDC) strategy as reported in this work, the need to work at high concentrations of porphyrin (as the zw-$TPPS_4$ itself regulates the pH of the medium in absence of any other acids which would provide for additional counteranions) together with the thin cuvettes used (alignment of fiber-like structures) and the slurry nature of the sample do not allow to reliably infer the chirality of the samples with a conventional CD spectrophotometer (see Figure ESI-3 below). In addition, further dilution of the sample in water results in a fast deaggregation of the porphyrin with the concomitant lose of the CD signal.

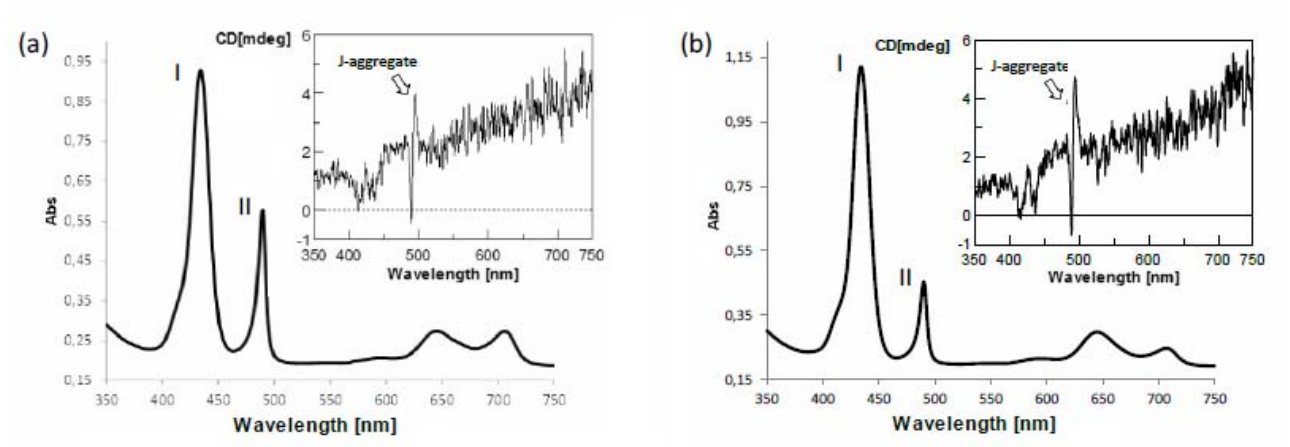


Figure ESI-3. UV-Vis and CD* (inset) spectra of (**a**) a typical zw-$TPPS_4$ sample obtained by dilution in water of the aqueous solution used in an organocatylic reaction, and (**b**) the same solution after the addition of two equivalents of isoindoline from an aqueous 0.07 M solution of the organic base. **I** corresponds to the signal of the monomeric acidic form of zw-$TPPS_4$ (overlapping with the H-aggregates absorbing at 420 nm) and **II** to its chiral homoassociated species. Both solutions are ~$4.0 \cdot 10^{-4}$ M in porphyrin and are mesured in cuvettes with a cell path of 0.1 mm.

CD spectra of the of the samples of 1:2 heteroaggregate between zw-TPPS$_4$ and isoindoline [zw-TPPS$_4$·(isoindoline)$_2$] in the chiral sign selection experiments

The supramolecular chirality sign of the homoassociated form of zw-TPPS$_4$ in the formation of the 1:2 heteroaggregate between zw-TPPS$_4$ and isoindoline [zw-TPPS4·(isoindoline)$_2$] (see above for the detailed description of the whole chiral sign selection process) was conveniently monitored by CD spectroscopy throughout the aggregation process before the final concentration was reached, using cells of different path lengths depending on the concentration of the sample (Figure ESI-4).

All CD spectra were measured in each experiment so as to assess whether or not a correlation could be established between the sign of the bisignated CD signals of the chiral aggregates and the detected enatiomeric excesses of the reaction products. When the same samples were measured in a Mueller Matrix spectrophotomer (Figure ESI-5), important contributions of linear dichroism were indeed detected; however, a true component of CD was still revealed in agreement with the result obtained with a conventional spectrophotometer. Despite the difficulty of measuring the CD spectra of these samples, in this case, however, the optimized procedure developed in order to select the final chirality of the zw-PPS$_4$ aggregates allowed us to monitor the chirality of the samples during the aggregation process, and thus we could measure the CD spectra at higher dilutions.

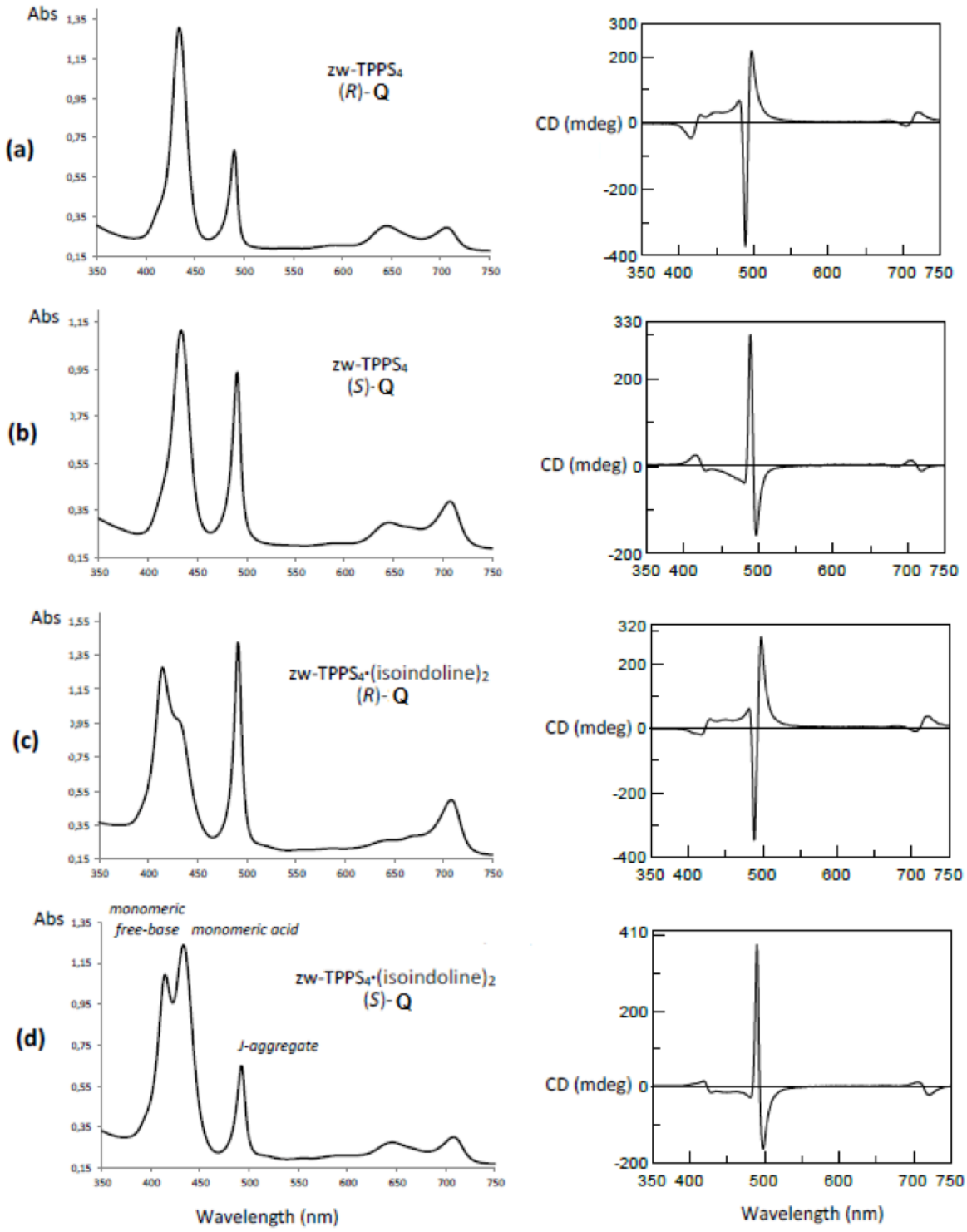


Figure ESI-4. UV-Vis (left) and CD* (right) of typical solutions zw-$TPPS_4$ samples extracted during the concentration process of the experimental procedure described above in which the supramolecular chirality has been selected either with (*R*)- or (*S*)-**Q** (Main Text). All spectra correspond to samples of ~$5.0 \cdot 10^{-4}$ M in porphyrin and are measured in cuvettes with a cell path of 0.1 mm. Note how the presence of isoindoline [(c) and (d)] results in partial reversible (if silanized glassware is used, see the text above) neutralization of the sample which then reverts to the acidic NH-protonated form upon further concentration to the final solution used for the organocatylitic reactions.

Measurements with Mueller Matrix Polarimetry

Mueller matrix polarimetry measurements where done on a UV-visible spectroscopic complete Mueller polarimeter. This apparatus, described in detail in ref.[8], measures simultaneously all elements of the 4x4 Mueller matrix thanks to four different photoelastic modulators. The solutions were sampled using 0.01mm pathlength cuvette cells and in the spectral range 350 nm-750 nm. The transmission Mueller-matrix measured at each wavelength was processed according to ref.[9], to calculate among others, the circular dichroism (CD) and linear dichroism (LD) shown below.

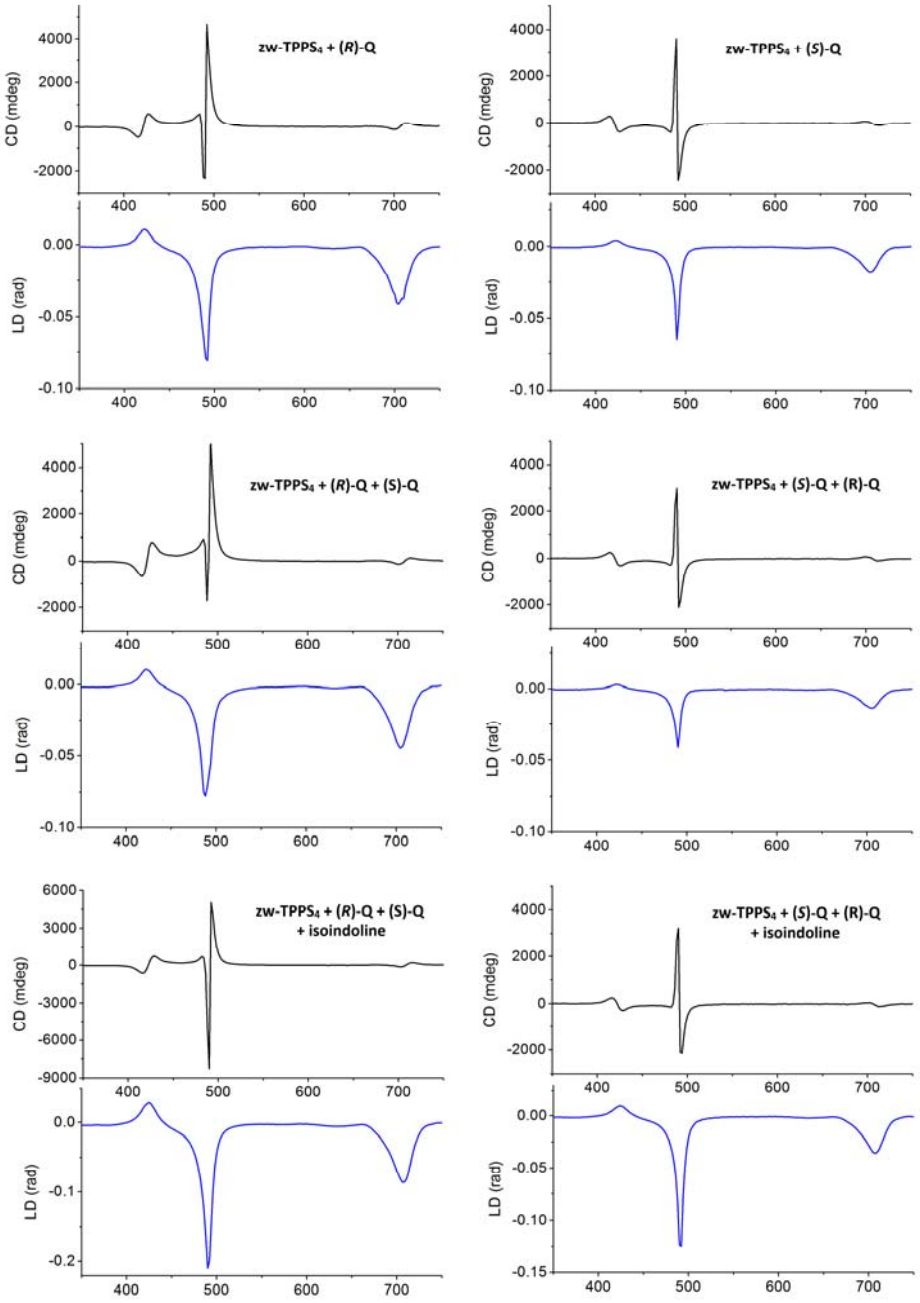


Figure ESI-5. Mueller Matrix Polarimetry allowed the unambigous assessment of the circular and linear dichroism. Top: CD and LD of the actual concentrated solutions used in the organocatalysis experiment using each eanantiomer of the chiral selector; Middle: the same solutions after the addition of the enantiomeric selector. Note that once the SMSM has taken place in the concentration process, the selectors have no effect whatsoever on the supramolecular chirality of zw-$TPPS_4$; Bottom: the same solution after the addition of isoindoline (in the same proportions as used in the organocatalysis experiments). The CD sign is not changed.

Chiral HPLC chromatograms of the Diels-Alder adducts.
Identification of the HPLC peaks

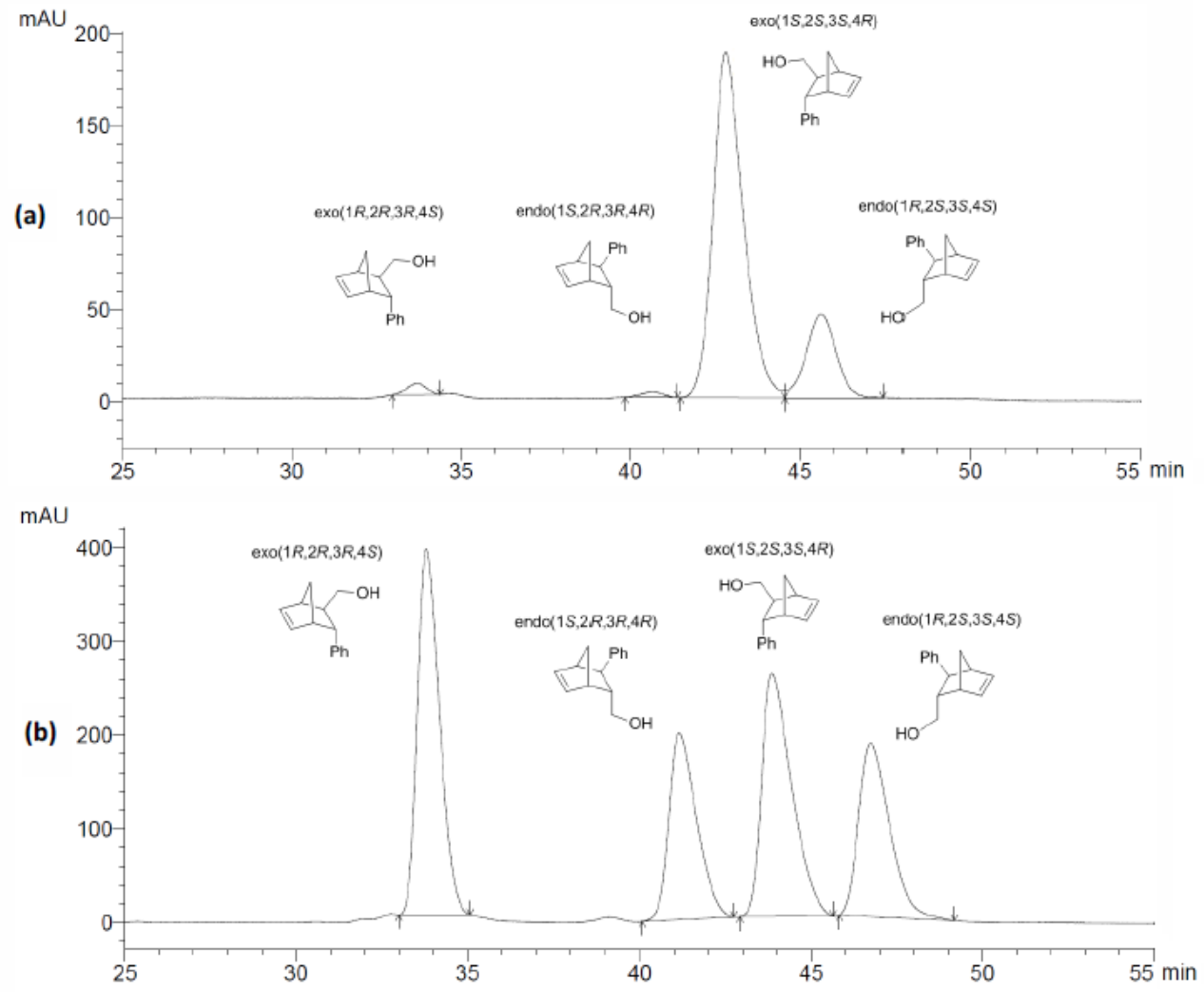
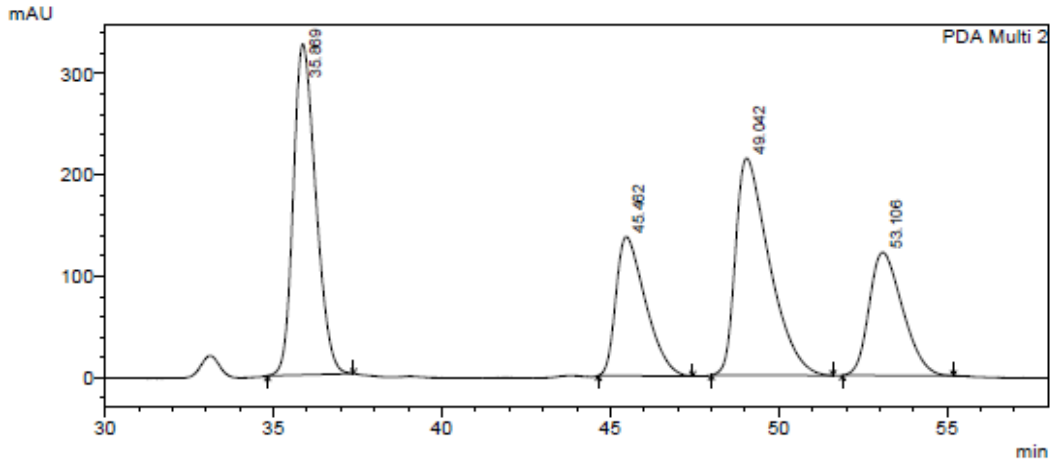


Figure ESI-6. Analytical chiral HPLC chromatograms. Phenomenex® I-Cellulose-5 column, 99.2:0.8 hexane/2-propanol, 1 mL/min, 25ºC, λ = 210 nm. **(a)** reaction catalyzed by an (*S*)-diarylprolinol derivative, ref.[4]; **(b)** of a typical sample obtained by using the chiral homoassociates of zw-$TPPS_4$·$(isoindoline)_2$ as the catalyst, prepared as described above.

HPLC chromatograms for entries in Table 1 of the main text

Entry 1a

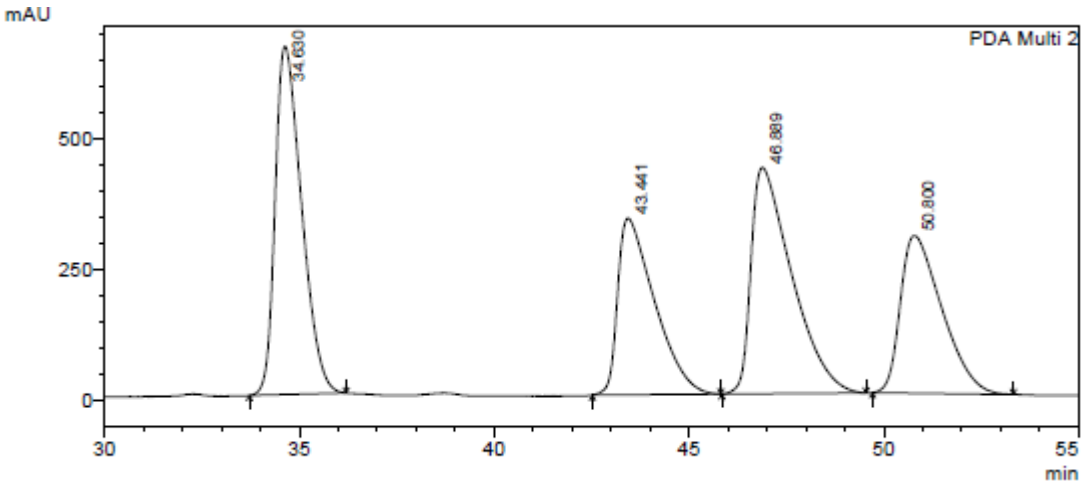


PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	35.869	15186955	326497	32.224	40.787
2	45.462	8429272	137737	17.885	17.206
3	49.042	15146322	214880	32.138	26.843
4	53.106	8367103	121388	17.753	15.164
Total		47129653	800502	100.000	100.000

Entry 1b

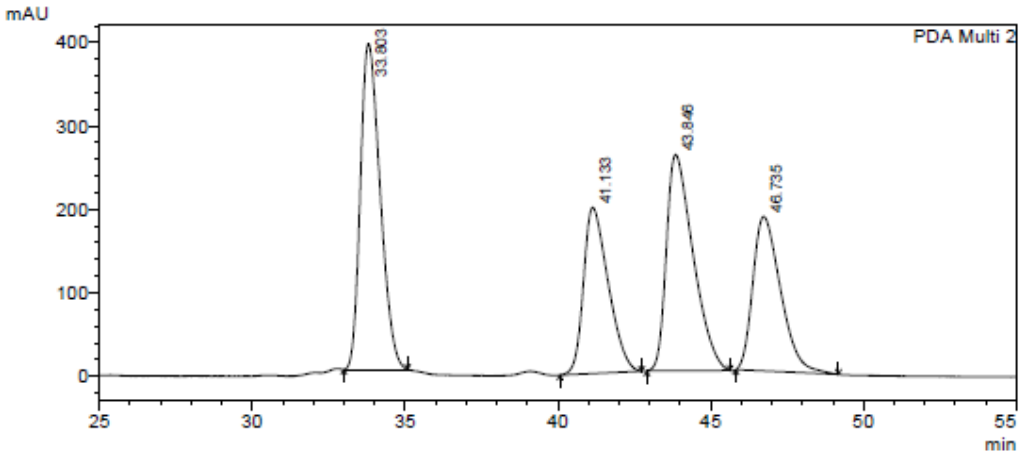


PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	34.630	31601771	667211	29.322	38.351
2	43.441	22289059	337978	20.681	19.427
3	46.889	31552269	432685	29.276	24.871
4	50.800	22333603	301858	20.722	17.351
Total		107776701	1739733	100.000	100.000

Entry 2a

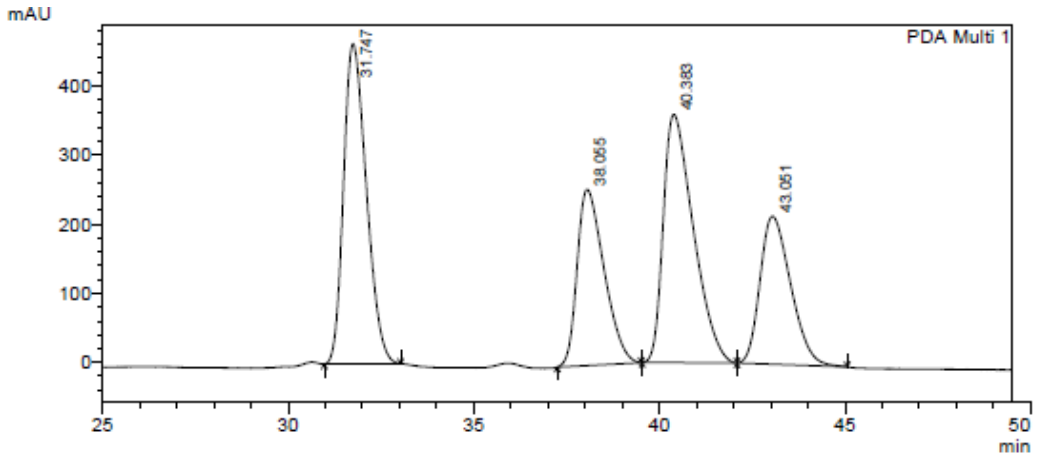


PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.803	17628240	390686	31.291	37.770
2	41.133	11189405	199100	19.862	19.248
3	43.846	15797197	259295	28.041	25.068
4	46.735	11721211	185290	20.806	17.913
Total		56336052	1034371	100.000	100.000

Entry 2b

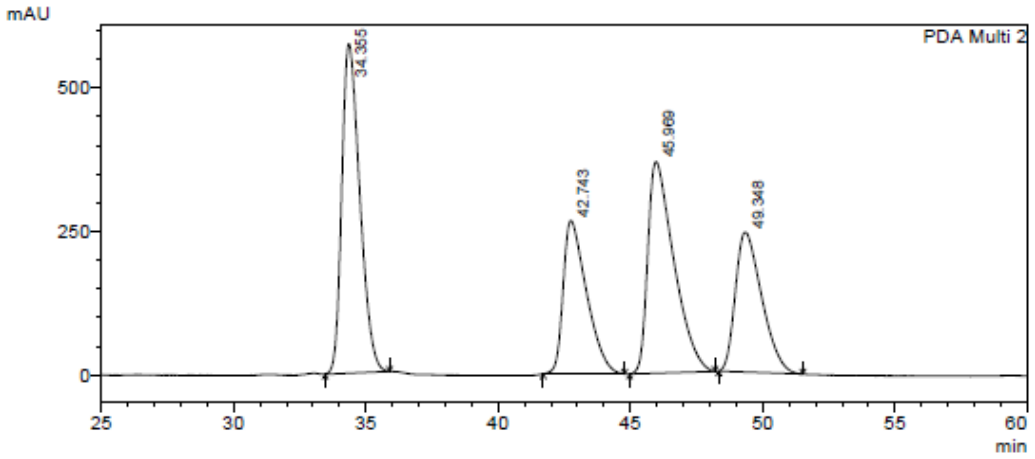


PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	31.747	19791084	463064	30.352	35.866
2	38.055	12854008	254757	19.713	19.732
3	40.383	20243806	359101	31.046	27.814
4	43.051	12316588	214158	18.889	16.588
Total		65205486	1291080	100.000	100.000

Entry 3a

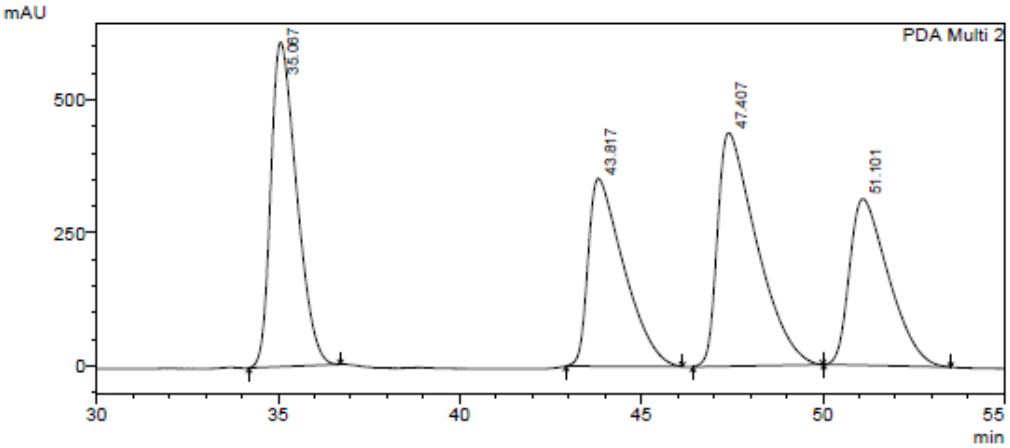


PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	34.358	27282045	573356	31.730	39.493
2	42.743	16351409	265786	19.017	18.308
3	45.969	25317639	368443	29.445	25.379
4	49.348	17031704	244194	19.808	16.820
Total		85982797	1451779	100.000	100.000

Entry 3b

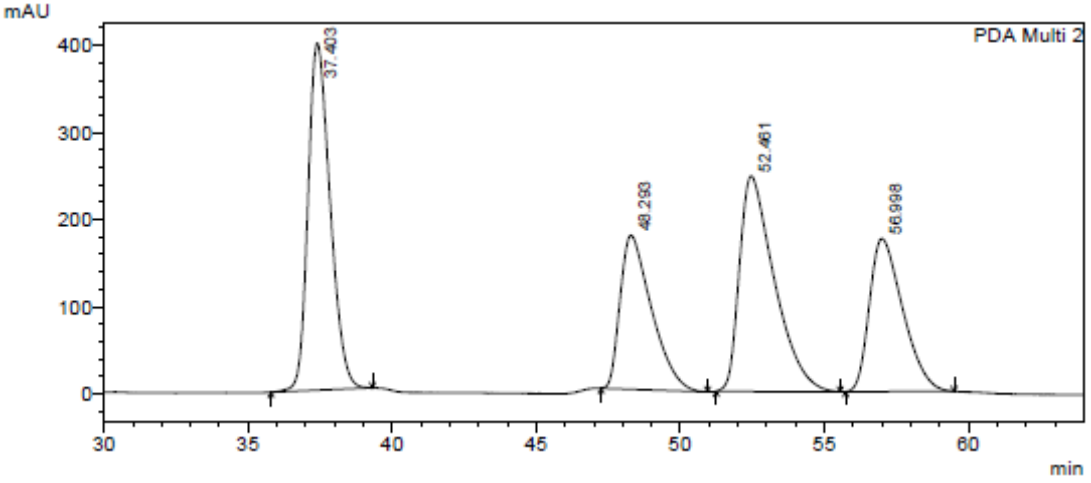


PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	35.067	29848009	607359	27.192	35.579
2	43.817	23847332	350197	21.725	20.515
3	47.407	32834343	437860	29.912	25.650
4	51.101	23238399	311639	21.170	18.256
Total		109768083	1707054	100.000	100.000

Entry 4a

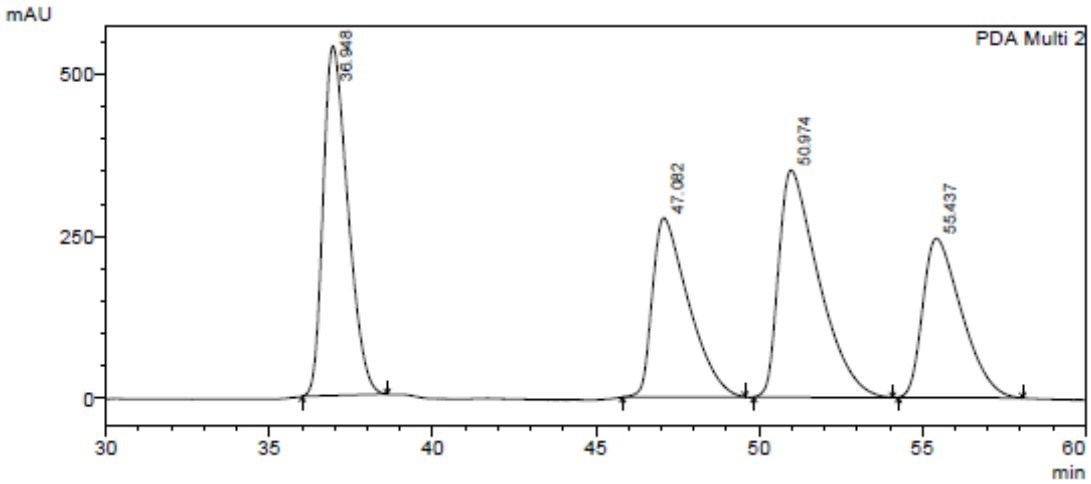


PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	37.403	21262424	398188	30.542	39.923
2	48.293	13359549	176651	19.190	17.711
3	52.461	20852861	247090	29.953	24.774
4	56.998	14142753	175458	20.315	17.592
Total		69617587	997388	100.000	100.000

Entry 4b



PeakTable

PDA Ch2 210nm 4nm

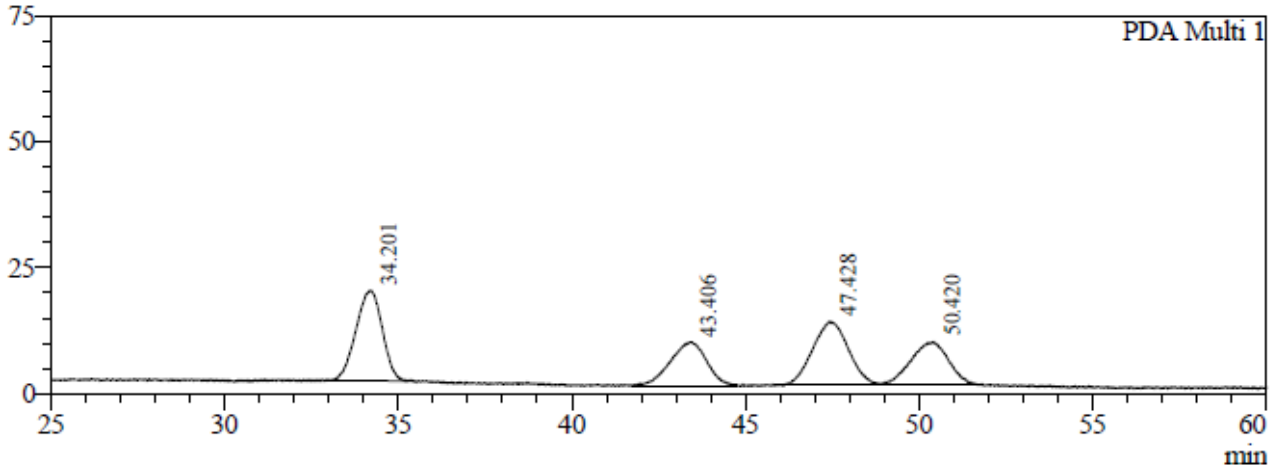
Peak#	Ret. Time	Area	Height	Area %	Height %
1	36.948	28396848	539036	28.398	38.195
2	47.082	21312867	276291	21.314	19.577
3	50.974	29906102	350375	29.908	24.827
4	55.437	20379153	245589	20.380	17.402
Total		99994969	1411292	100.000	100.000

HPLC chromatogram of the adducts obtained in a reaction using zw-TPPS$_4$·(isoindoline)$_2$ without the use of any chiral selectors (unpolarized SMSB)

In the following example (entry 5 in Table ESI-2), the reaction was carried out as described above (page ESI-11, footnote [a] of Table ESI-2), using the zw-TPPS$_4$ as obtained in the synthetic procedure described on page ESI-4.

Conversion: 22%
exo:endo ratio: 57:43
ee$_{exo}$: 2.3±0.6 (2*R*,3*R*); ee$_{endo}$: 2.3±0.6 (2*S*,3*S*)
zw-TPPS$_4$ CD: bisignated (+/-)*

Note that the enantiomeric preference is in accordance with the signal of the CD spectra (i.e. supramolecular chirality of the heteroaggregate catalysts) as reported in Table 1 of the main text.



PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	34.201	947938	17924	30.339	37.545
2	43.406	621240	8611	19.883	18.037
3	47.428	904812	12622	28.959	26.438
4	50.420	650505	8584	20.820	17.981
Total		3124496	47741	100.000	100.000

* CD-signals of the bisignated exciton coupling bands at 489 nm corresponding to the J-aggregate of zw-TPPS$_4$ in the zw-TPPS$_4$·(isoindoline)$_2$ heteroaggregates; the signs are reported from longer to shorter wavelengths.

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