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Large scale chirality transduction with functional molecular materials

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ABSTRACT: Transduction of chiral information can be achieved at different length scales. Among all possible approaches, we propose in this work a straightforward concept to transfer chiral features from the molecular level to the shape of macroscopic objects by combining the concepts of inherently chiral oligomers and bipolar electrochemistry. Hybrid freestanding lamellar films, composed of polypyrrole and the two oligomeric antipodes of a chiral monomer, are exposed in solution to a chiral target molecule (*i.e.* L- and D-DOPA) in the presence of an electric field. This leads to an electrochemically induced deformation of the film, which *in fine* results in one or the other of two macroscopic enantiomorphs, depending on which stereoisomer is present in the solution.

INTRODUCTION

Chirality can be defined at different length scales, ranging from the molecular to the supramolecular and macroscopic scale[1]. Local chirality refers to the molecular scale, and arises from variations in the configuration of a molecule. Global chirality is defined with respect to conformations at bigger length scales, such as in oligomers, polymers and supramolecular assemblies. Macroscopic chirality refers to micrometer or larger scales, including crystals and biological structures.

The transmission mechanism of chirality from nano- to meso- and macroscopic length scales is rather complex and not yet well understood[1]. Since the first resolution experiments carried out by Pasteur in 1848, many studies have addressed this fascinating topic of chirality transfer from the molecular scale to structures at the macroscopic level[2-4]. Various biological materials, such as plant tendrils, flower petals and snail shells, exhibit chiral growth. In these natural materials, there are chiral elements that lead to the formation of various chiral morphologies at the macroscopic scale with a specific handedness, either right or left. The investigation of the mechanisms related to chiral growth of biological materials is a fundamental issue, not only in biology, but also closely connected to materials science and technology fields. Scientists have explored chirality transmission mechanisms at different length scales with several concepts that in general try to mimic what happens in nature.

One of the way to transfer chirality could be through chiral recognition and/or enantioselective interactions between molecules; really important clue in biological, chemical and industrial applications[5]. In the chemical field, these processes are usually studied by optical, spectroscopic and electrochemical methods. The transformation of the chiral signal into macroscopic changes in the properties of a material is really attractive for the directly connection to other practical applications like chiral separation, catalysis and functional devices[6-7].

Among the synthetic systems that mimic natural ones, chiral liquid crystals[8], chiral metamaterials[9], chiral catalysts[10], chiral bio-sensors[11], and chiral separation materials[12] need to be cited.

In particular electronically conducting polymers are one of the most popular materials classes employed in advanced devices because of their good electron transfer and their easy functionalization to tune the material properties.[13] They can be prepared trough many protocols, either by *in situ* electrodeposition from suitable monomers or by chemical synthesis followed by physical deposition processes. These materials can concurrently act as receptors and transducers, and be directly endowed with chirality, or a chiral monomer could be integrated during polymerization. In this way, the chiral signal is transferred from the guest chiral molecules, or the polymer itself, to the macroscopic features of the material. On the other hand, these properties can also be modified by external stimuli (solvent[14-15], temperature[16], pH[16], electric field[17]) that directly influence the chiral conformation of the polymer chains at the macromolecular level.

Enantioselective interactions between chiral molecules and chiral conducting polymers could induce visible changes at the macroscopic scale; many polymers/oligomers have been so far developed mostly including chiral thiophene, pyrrole and aniline derivatives. Some of these materials have been tested as chiral electrodes in enantioselection discrimination processes in advanced sensing electrochemical devices.[18] In most of these attempts the electrochemical enantioselectivity has been only partially achieved. Enantioselectivity manifestations are weak or labile and the kind of response (*e.g.*, in terms of current or potential *vs* concentration) seems unsuitable for purposes of recognition and quantification by a single selector of either configurations of the probe enantiomer in mixture. A disadvantage could be that in most cases the stereogenic elements are either stereocenters localized in pendants external to the main backbone responsible of the functionality of the material[19] or a "secondary" chiral structure easily lost as a function of operating conditions,[20] or a chiral shape derived from external templating agents.[21]

In 2010 Sannicolò *et al.* designed a monomer[22] with 3,3'-bibenzothiophene as a central scaffold, endowed with inherent chirality,[23]to be employed as racemic co-monomer in electrosynthesis. In other reports, tests were carried out using the individual enantiomers of this chiral molecule, separated by chiral HPLC.[24] Their electrooligomerization resulted in chiral electrode surfaces, able to discriminate the enantiomers of chiral species by differences in peak potential recorded by cyclic voltammetry.[25-26] This is a true advantage from an analytical point of view, because it is possible to achieve discrimination of racemic mixtures of the analyte, in contrast to most of the approaches discussed above for which the recognition is only based on differences in current intensity[27-29].

In this context, a new concept of absolute chirality transfer from the molecular to the macroscopic level has been reported very recently[30], based on the chirality dependent induction of motion of a hybrid polymer film. Analog to previous works[31-32], bipolar electrochemistry was used as a driving force to trigger the preferential oxidative conversion of an enantiomer at one extremity of the polymer film, whereas at the opposite extremity the polymer undergoes a reduction, accompanied by site selective swelling and shrinking. The resulting deformation of the film can then be used as a readout of chiral information. In contrast to previous studies[33-34], the combination of the robust concept of inherent chirality with the electromechanical proprieties of polypyrrole (Ppy), allowed the development of a bipolar electroactuator with a true chirality-dependent on-off behavior[30]. The enantiopure inherently chiral oligomer was deposited on one side of a Ppy strip and used as bipolar electrode able to react differently, with a yes-no response, to the enantiomers of a redox active chiral analyte (L- or D-DOPA). The difference in terms of oxidation potentials between L- and D-DOPA is sufficient to observe the electromechanical actuation of Ppy only in the presence of the enantiomer that is easier to oxidize. Furthermore, the actuation is proportional to the concentration of the "good" enantiomer, and completely independent of the presence of the other antipode[30].

In the present work, we intend to make a further step towards the transfer of chiral information from the molecular to the macroscopic scale. In particular, the aim is to trigger by bipolar electrochemistry the deformation of a specifically designed hybrid material in such a way that it leads to the formation of two macroscopic objects, being not superimposable mirror images of each other.

RESULTS AND DISCUSSION

The electrooligomerization of enantiopure inherently chiral monomers on substrates like gold or glassy carbon in different media (aqueous media and organic solvents) leads to enantiopure surfaces with a well-pronounced enantioselection ability[18-21]. In order to confirm in a first step that the oligomers show chiral recognition properties also when they are generated on a Ppy film, we carried out tests with Ppy films, modified with (*R*) or (*S*) enantiopure oligomer layers, analog to what has been reported earlier[25]. The inherently chiral monomer chosen for this purpose was 2,2'-bis[2-(5,2'-bithienyl)]-3,3'-bithianaphthene (BT_2T_4), already well-known and characterized by Mussini *et al.* [18-21]. It is constituted of 3,3'-bibenzothiophene as an atropisomeric central scaffold, with a sufficiently high racemization barrier to yield stable enantiomers, and functionalized with two 2,2'-bithiophenic units featuring two α-homotopic positions of the terminal thiophene rings, granting a regioregular oligomerization. In preliminary tests, Ppy films were deposited by chronopotentiometry on gold coated glass slides and then covered with oligo-(*R*) or oligo-(*S*)-BT_2T_4 according to a literature procedure[30-31]. The final hybrid films were peeled off from the gold-coated glass slide and used for a first, more classic enantiorecognition tests, performed by differential pulse voltammetry (DPV) in the presence of aqueous solutions of 5 mM L- or D-DOPA and lithium perchlorate 0.1 M.

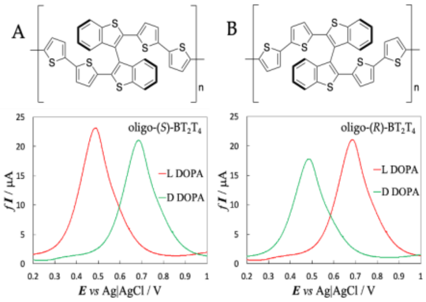
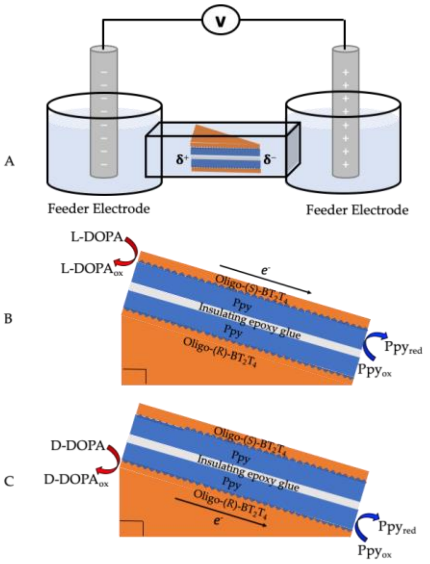


Figure 1. Top: Chemical structures of the enantiopure oligo-(*S*)- BT_2T_4 (A) and oligo-(*R*)-BT_2T_4 (B) molecules employed in the enantiorecognition tests. Bottom: Differential pulse voltammetry signals of the enantioselective electrooxidation of 5 mM L- or D-DOPA in water and 0.1 M $LiClO_4$ on a hybrid polymer layer composed of A) Ppy + oligo-(*S*)-BT_2T_4 and B) Ppy + oligo-(*R*)-BT_2T_4.

From Figure 1A, it is obvious that the (*S*)-hybrid surface is preferentially reacting with L-DOPA, with a peak-to-peak separation between the two enantiomers of about 200 mV. The results are also perfectly coherent when the opposite configuration of the BT_2T_4 oligomer is deposited. The (*R*)-hybrid allows a preferential oxidation of D-DOPA. Consequently, at ~0.45 V vs. AgCl/Ag it is possible to selectively electrooxidize only one of the two DOPA enantiomers, depending on which oligomer configuration is deposited on Ppy.

If this hybrid material is used as an electrode in a bipolar electrochemistry experiment, it should be possible to transform exclusively L- or D-DOPA on the positively polarized extremity of the film if the polarization potential difference is fine-tuned to a value that is just enough to oxidize the "good" enantiomer. At the other extremity of the bipolar object, a charge compensating reduction reaction has to occur simultaneously. Considering that Ppy reduction occurs at about – 0.25 V vs. AgCl/Ag, the theoretical threshold of the polarization potential difference between the two extremities of the bipolar electrode should be around 0.65 V in order to activate both reactions at the same time.

The schematic cell configuration employed in the bipolar experiments is represented in Scheme 1A. Two graphite rods are used as feeder electrodes and connected to a power supply. The bipolar electrode has a specific shape and composition in order to allow transmission of chiral information from the molecular to the macroscopic scale. Actually, the overall geometry has to be a scalene triangle with its two faces being constituted of (*R*)- and (*S*)-oligo-BT_2T_4, electrodeposited on Ppy, respectively. They are combined in a sandwich-type structure with an insulator in between in order to prevent electrons from passing from one face to the other (Scheme 1B and C). The final triangular object is placed directly at the bottom of the cell without using any kind of support. The solution contains L- or D-DOPA (5 mM) dissolved in water and 0.1 M $LiClO_4$. When a suitable electric field is applied, only one of the two enantiopure faces is able to react as a function of which analyte enantiomer is present in the solution.



Scheme 1. A) Schematic illustration of the bipolar cell used for the experiments of chirality transmission through space. The distance between the feeder electrodes is 5 cm and the length of the bipolar electrode is 1.0 cm. The solution contains 5 mM L- or D-DOPA in water and 0.1 M $LiClO_4$. B) and C) Magnifications of the sandwich like bipolar electrodes used for the experiments and the principle responsible for their operation. When L-DOPA is present in solution, only the oligo-(S)-BT_2T_4 layer is able to react (B) and *vice versa* when D-DOPA is the analyte (C).

An electric field of proper amplitude leads to a δ^+ and δ^- polarization at the extremities of the triangle. Under these conditions, one of the antipodes of DOPA gets selectively electrooxidized at the positively polarized end, while at the δ^- side Ppy is reduced. The latter is accompanied by an uptake of solvated Li^+ cations that enter the polymer film in order to maintain electroneutrality[35-37] (dodecylbenzene sulfonate anions, inside the polymer, are sufficient bulky to remain into the polymer). This process induces a face-selective swelling of the chiral object, depending on the stereochemistry of both the chiral analyte in solution and the chiral oligomer. Shrinking would occur only upon a reoxidation of the film, but in our specific case it is not possible considering that the extremity of the film which shows the deformation is negatively polarized, so only a reduction reaction is possible.

The result of this asymmetric electromechanical bending is that the hybrid polymer film starts curling in one direction or the other. As the initial geometry is a scalene triangle, meaning that no sides and no angles are equal, the final curved objects have no plane of symmetry and thus are macroscopic enantiomorphs as illustrated in the following.

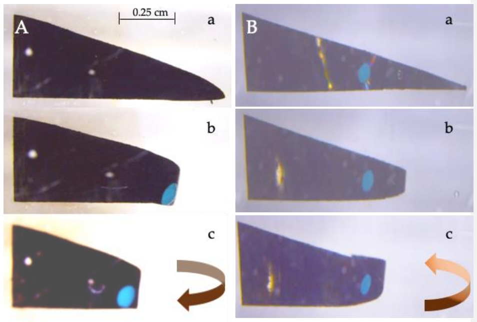


Figure 2. Hybrid lamellar electrode strips exposed to an aqueous solution of 5 mM D-DOPA and 0.1 M $LiCO_4$. A) (*R*)-oligo-BT_2T_4 is oriented towards the backside. B) (*R*)-oligo-BT_2T_4 is present at the front side. (a), (b) and (c) illustrate different stages during the bending process. A blue varnish dot is placed at the face modified with (*R*)-oligo-BT_2T_4 to guide the eye during the movement induced by the application of an electric field of 0.6 V cm^{-1}.

The system was optimized considering that the initial film has not to be too thick to guarantee *i)* the electroactivity, *ii)* the diffusion of Li^+ ions inside the PPy matrix upon reduction and *iii)* the flexibility that allows the object deformation by the electric field. The thickness of 200 μm used in the current work (see Fig SI 1) is a good compromise in order to satisfy the different requirements. The deposition procedure of Ppy together with the thickness were already optimized and widely discussed in previous works[30-32]. The insulating layer, which has a thickness of 100 μm, is as thin as technically possible in order to not introduce additional stiffness to the hybrid film. The capping enantiopure oligomer layer is extremely thin (less than 10 μm, Figure SI 2); it only serves as molecular recognition element, an almost monolayer-type modification would be still sufficient to ensure enantioselectivity.

Placing the hybrid object in the bipolar cell in the presence of L- or D-DOPA and applying an electric field of 0.6 V cm^{-1}, the direction of curling is controlled by the chiral face involved in the electrooxidation, as illustrated in Figure 2 (see also Video S1 and S2). A blue spot of varnish has been added in order to better visualize the curling and it is positioned at the face modified with (*R*)-oligo-BT_2T_4 to guide the eye. Both chiral hybrid films were exposed to a solution containing 5 mM D-DOPA and

0.1 M $LiClO_4$. In Figure 2A, the (*R*)-oligo-BT_2T_4 is present at the back side (blue spot not visible in (a)), whereas in Figure 2B the same oligomer was deposited on the front side of the hybrid object. In both cases, electrooxidation of D-DOPA occurs on the face modified with the (*R*)-oligomer, causing a swelling of this part of the bilamellar strip. *In fine* this results in a controlled bending of the film, either towards the front (Figure 2A b-c, the blue spot which initially was not visible moves towards the front) or backwards (Figure 2B b-c, the initially visible blue spot moves towards the backside).

Both experiments can also be followed in real time by watching the bending of the hybrid sheets from the side (Figure 3). In this case, the blue spot of varnish has always been added to the upper part of the lamellar object. In Figure 3A the (*R*)-BT_2T_4 oligomer is localized at the bottom face of the sheet in both cases ((a) and (b)). If these two identical objects are exposed to the molecular antipodes of DOPA, the bending occurs in opposite directions. In case (a), the bottom layer of oligomer reacts with the D-DOPA present in solution, because at the chosen polarization potential only this one can react with D-DOPA (see CVs in Figure 1 and Supporting Video S3). This provides the electrons necessary for the reduction of Ppy. Consequently the bottom Ppy layer swells and thus starts bending upwards. For case (b), with L-DOPA in solution, it is the upper layer of the hybrid film, composed of (*S*)-oligo-BT_2T_4 and Ppy, which becomes active. Therefore, the upper part starts swelling and the film is bending downwards. A perfectly complementary scenario of chiral selection is illustrated in Figure 3B. In this example the same enantiomer (D-DOPA) is present in both experiments (a) and (b), however the hybrid layer has a different initial orientation. In (a) the (*R*)-BT_2T_4 oligomer is facing down, whereas in (b) it is (*S*)-oligo-BT_2T_4 which constitutes the bottom layer. The induced bending is analog to what has been observed in Figure 3A, but based on different diasteromeric couples, as it is possible to change the chiral configuration of either the probe or of the selector to achieve the same result. In other words, the chiral information can be propagated to the macroscopic scale in two different ways. In the first case (Figure 3A) the chiral recognition occurs between the two molecular antipodes of the probe (D-DOPA and L-DOPA) and one given configuration of the selector. In the second case (Figure 3B) two different selector configurations interact with one and the same enantiomer (D-DOPA). Both situations lead to opposite bending due to the diasteromeric interactions between probe and selector.

Since the deformation of PPy is reversible and the composite object is constituted by two faces of (*R*)- and (*S*)-oligo-BT_2T_4, respectively, we can assume that the curling of the same object can be tuned in different directions by changing the configuration of the chiral probe dissolved in solution.

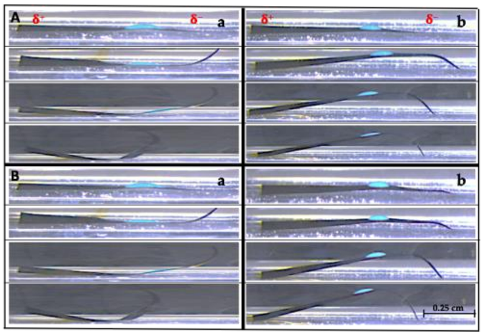


Figure 3. Side view of the triangular hybrid polymer objects, when an electric field of 0.6 V cm^{-1} is applied. A sequence of four time laps images, extracted from Supporting Video S3, are shown for each panel. A) The (*R*)-BT_2T_4 oligomer is orientated towards the bottom and the object is exposed to a 0.1 M $LiClO_4$ solution containing either (a) D-DOPA or (b) L-DOPA. B) The (*R*)-BT_2T_4 oligomer is orientated towards either (a) the bottom or (b) the top and the object is exposed to a 0.1 M $LiClO_4$ containing in both cases 5 mM D-DOPA.

The analyses of the bending angle and the curvature *vs.* time, in the presence or L- or D-DOPA in solution with (*R*)-BT_2T_4 oligomer orientated towards the bottom (Figures SI 3 and SI 4), have shown that there is an almost linear increase of both the figures of merit. The increment is less steep at lower range of time according to the object stiffness induced by the presence of the blue paint.

At the end of the bipolar experiments, when the curling is completed, the freestanding polymer films can be removed from the solution and dried. The resulting objects are shown in Figure 4. The polymer film illustrated in Figure 4a is the result of the curling experiment depicted in Figure 2A, whereas Figure 4b shows the final configuration of the object from Figure 2B. (*R*)-oligo-BT_2T_4 was located at the front side of the triangle, whereas in the other case it was at the backside (Figure 2A and 2B, respectively). Therefore, the bending occurs in opposite directions. The same type of experiments could be also carried out by depositing the (*R*)-oligo-BT_2T_4 on the same side of the two triangles, but with the objects being exposed to the two enantiomers of DOPA, separately. Both type of experiments lead to identical results, based on diastereomeric interactions.

The final two objects are specular enantiomorphs, endowed with inherent chirality due to the particular geometry of the scalene triangles having three different angles and three edges of different length. This means that the molecular chirality has been successfully transferred to the macroscopic scale in a straightforward way.

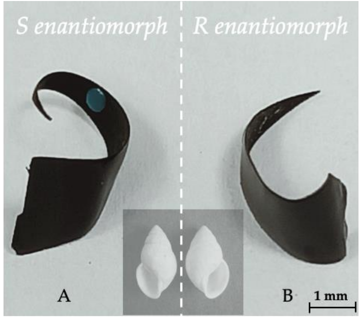


Figure 4. Picture of the two (*R*)- and (*S*)-enantiomorphs recovered at the end of the bipolar experiments illustrated in Figure 2, illustrating the transmission of molecular chirality to the macroscopic scale (scale bar 1 mm)

CONCLUSION

We have confirmed the robustness of the concept of inherent chirality that allows conferring intrinsic chiral features to the materials used as building blocks of hybrid bilayer objects. Following this concept, it is possible to propagate chiral information along different length scales. After starting from the molecular level with the inherently chiral monomers, the next step encompasses the supramolecular scale, via a transmission into helical macromolecular structures during electrooligomerization, and culminates in macroscopic chirality represented by the controlled generation of enantiomorphs through chirospecific curling, triggered by bipolar electrochemistry. Such an artificial version of macroscopic enantiogenesis, based on the synergy of well-chosen molecular ingredients and physico-chemical engineering, can be considered as a model system for the transmission of chiral information through space in natural systems.

MATERIALS AND METHODS

Synthesis of the polypyrrole films. Pyrrole monomer (0.2 M) was dissolved in Milli Q water with dodecylbenzene sulfonate (0.25 M). After complete dissolution of both components, two gold coated glass slides were positioned parallel in a beaker. The beaker was filled with 12 cm^3 of this solution and one gold coated glass slide was used as a working electrode while the other one as counter electrode and Ag/AgCl (3M KCl) was the reference electrode. A fixed current of 4 mA was applied for 1.5 h for the polymerization of pyrrole. After polymerization, the polymer coated substrate was washed with water, dried and used for further oligomerization of 2,2'-bis[2-(5,2'-bithienyl)]-3,3'-bithianaphthene chiral monomer.

Electrosynthesis of enantiopure oligo-(*R*)- or oligo-(*S*)-2,2'-bis[2-(5,2'-bithienyl)]-3,3'-bithianaphthene (oligo-(*R*)- or (*S*)-BT_2T_4). The electrosynthesis of enantiopure oligo-(*S*)-BT_2T_4 and oligo-(*R*)-BT_2T_4 was carried out by employing the polypyrrole coated substrate as working electrode in a small beaker containing 10 cm^3 of 0.1 M solution of lithium perchlorate ($LiClO_4$) in acetonitrile (MeCN) and the (*R*)- or (*S*)- enantiopure monomers at 5mM concentration. The counter electrode was a platinum grid together with an Ag/AgCl reference electrode. Oligo-(*S*)-BT_2T_4 and oligo-(*R*)-BT_2T_4 were synthetized by chronopotentiometry at a fixed current value of 4 mA for 40 minutes onto the whole rough polypyrrole surface. After deposition of the oligo-(3,3'dibenzothiophene)-polypyrrole hybrid films, they were peeled off from the gold electrode and then properly cut in a triangular shape, with a 90° angle. In this way two bilayer systems were obtained: i) one scalene triangle with (*R*)-oligo-BT_2T_4 on top of the Ppy and ii) one scalene triangle with (*S*)-oligo-BT_2T_4 on top of the Ppy. The two triangles were combined using expoxy glue with the smooth Ppy sides (the ones without the oligomers) facing each other. The resulting hybrid sandwich (see Scheme 1) was used as a bipolar electrode.

SEM analysis of the hybrid sandwich electrode. SEM experiments were carried out using a Hitachi TM-1000 tabletop microscope. A SEM micrograph of the cross section of the entire sandwich-like triangle is provided in the SI (Figure SI 1). Another SEM micrograph of the cross section of the Ppy + enantiopure oligomer composite film is depicted in Figure SI 2.

Differential pulse voltammetry (DPV) experiments. DPV experiments were carried out in a beaker, used as electrochemical cell, containing the enantiomers of L- or D-DOPA (5 mM) dissolved in water and 0.1 M $LiClO_4$. The reference electrode was Ag/AgCl and a platinum grid the counter electrode. The working electrodes were hybrid electrodes composed of an oligo-(*S*)-BT_2T_4 layer or an oligo-(*R*)-BT_2T_4 layer, deposited on a freestanding Ppy film. This film was carefully isolated on the backside with varnish and connected with copper tape to the potentiostat. The optimized DPV parameters used for recording the voltammetric signals of L- or D-DOPA were: step potential 10 mV, modulation amplitude 60 mV, modulation time 40 ms and interval time 200 ms.

Bipolar curling experiments. For bipolar curling experiments, enantiopure (*R*)- or (*S*)-oligo-(3,3'-dibenzothiophene)-polypyrrole hybrid triangles were placed in the center of the bipolar cell without any support. Two graphite feeder electrodes were positioned at the extremities of the cell (5 cm distance). 0.1 M $LiClO_4$ was used as supporting electrolyte to provide a sufficient amount of ions for charge compensation in the conducting polymer during bipolar actuation in the presence of 5 mM L- or D-DOPA.

The chirality controlled deformation was recorded using a macroscope (LEICA Z16 APO) in video mode.

Movie data treatment was carried out with the help of image J software.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Video S1 Hybrid lamellar electrode strip exposed to an aqueous solution of 5mM D-DOPA and 0.1 M $LiCO_4$, (*R*)- oligo-BT_2T_4 is deposited at the back (.avi)
Video S2 Hybrid lamellar electrode strip exposed to an aqueous solution of 5mM D-DOPA and 0.1 M $LiCO_4$, (*R*)- oligo-BT_2T_4 is deposited at the front (.avi)
Video S3 Hybrid lamellar electrode strips with (*R*)-BT_2T_4 oligomer at the bottom exposed to an aqueous solution of either 5 mM D-DOPA or 5mM L-DOPA (.avi)

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Author Contributions

S.A. and B.G. designed and performed the experiments; wrote and edited the manuscript. A.K. proposed the research project, provided resources, designed experiments and edited the manuscript.
T.B. designed the inherently chiral monomers, G.B. synthetized the inherently chiral monomers, R.C separated the enantiomers of the inherently chiral monomers by chiral HPLC.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

(*R*)- or (*S*)-2,2'-bis[2-(5,2'-bithienyl)]-3,3'-bithianaphthene ((*R*)- or (*S*)-BT_2T_4); differential pulse voltammetry (DPV); L- or D-3,4-dihydroxyphenylalanine (L- or D-DOPA); polypyrrole (Ppy); lithium perchlorate ($LiClO_4$); potassium chloride (KCl), acetonitrile (MeCN)

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