Absolute Chiral Recognition with Hybrid Wireless Electrochemical Actuators

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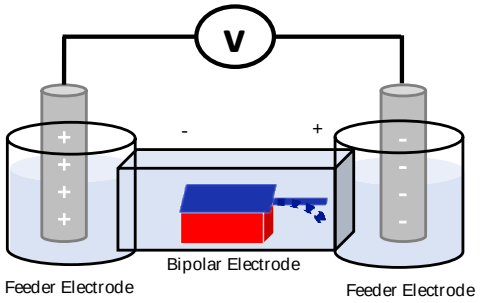
KEYWORDS absolute chiral recognition • wireless electrochemistry • hybrid electrochemical actuator • inherently chiral conducting polymer • enantiomeric excess determination

ABSTRACT: Chiral discrimination is of crucial importance for many applications, including drug cross checking and electronic tongue type devices. In a typical sensing scheme, an enantiomeric selector is combined with an appropriate transduction mechanism. We propose here a hybrid material composed of an electrically conducting oligomer *i.e.* oligo-(3, 3'-dibenzothiophene) bearing inherently chiral features, and polypyrrole as a support which can undergo electrochemical actuation. The combination of both leads to a freestanding film that is addressable in a wireless way based on the principle of bipolar electrochemistry. The induced redox reactions lead to well-pronounced actuation when DOPA with the right chirality is present in solution as a model analyte, whereas absolutely no electromechanical response is measured for the wrong enantiomer. This constitutes a straightforward and absolute read out of chiral information where the amplitude of actuation is correlated with the concentration of the analyte. Optimization of the scheme results in highly efficient bending, and thus opens up new directions in the field of chiral technologies.

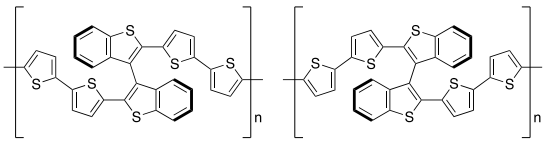
Chiral discrimination is of vital importance in analytical chemistry as it is highly desired, among others, in the pharmaceutical industry and forensic or environmental science to test analytes of pharmaceutical and biological interest.[1-6] In the case of chiral drugs, often only one enantiomer is effective and useful for the consumer, whereas the antipode is inactive or even can have detrimental effects. Therefore, selective recognition of enantiomers is the basis of both, drug production and quality control.[5, 7-8] Among all the different analytical approaches proposed in this context, electrochemical ones look potentially very attractive, with intrinsic advantages including selectivity, sensitivity, low cost and easy transduction of recognition events and signal processing.[9-11] In this context it is very interesting to combine electrochemistry with chirality in order to achieve a high degree of selectivity and sensitivity. Recently, certain oligomers in which the molecular function responsible for electroconductivity coincides with the 3D molecular scaffold responsible for chirality (inherently chiral oligomers) emerged as a new tool for chiral voltammetry. In this case, differentiation of the enantiomers of a chiral analyte is possible in terms of variations of peak potential values, rather than measuring different current intensities enabling effective enantiorecognition.[12] When this feature is combined with a linear dynamic range for currents it is also possible to determine enantiomeric excesses in mixed solutions, containing different ratios of antipodes of a chiral probe. In fact, during oligomerization, the inherent chirality of the oligomers is translated into helical foldamer-like macro- or supramolecular structures.[13] The obtained oligomers are easy to prepare and highly robust in comparison with other materials investigated for implementation of chirality on electrode surfaces (the description of the advantages related to the implementation of this strategy instead of other approaches for the obtainment of enantioselective surfaces is detailly explained in literature in different previous works).[1] Recently Arnaboldi *et al.* demonstrated that enantiopure inherently chiral oligomers with an atropisomeric core (*e.g.*, 3,3'-bibenzothiophene,[12] 2,2'-biindole[13] and 3,3'-bithiophene[14]) allow recognizing chiral probes with different chemical nature in terms of difference in formal electrochemical potential values, combined with the possibility, in some cases, to determine enantiomeric excess. [15] The perspective of this concept, and the aim of the present contribution, is to develop low cost, portable and wireless transducers for a quick and absolute detection of chiral information. Designing a wireless readout scheme of chiral information requires two essential ingredients: one for the enantioselective electron transfer process and the other one for transduction. To simplify the system, a wireless mode of interfacing has recently been considered to facilitate electrochemical detection, especially when having in mind the increasing popularity of smartphones combined with a portable potentiostat.[16-17] However, for classic electrochemical transduction, the detector electrode has to be

wired to the power supply. In contrast, when using a bipolar electrochemistry mode, an electric field is generated between two feeder electrodes to induce a polarization of a remotely placed bipolar electrode which undergoes the electrochemical transformation. The current passing through the bipolar electrode as a function of the concentration of electroactive molecules can be evaluated with different approaches such as electrochemiluminescence, electrodissolution, concentration enrichment of charged analytes and electromechanical deformation etc.[18-31] The optical readout of electrochemical activity provides a low cost measurement of different species and has various other advantages like the easy detection of color changes or light emission, eventually with the naked eye, useful for chemical imaging and in the frame of massive parallel analytical arrays.[32-36] Apart from light emission, colour changes and fluorescence, mechanical deformation is an interesting alternative for the optical visualization of signals. It has been recently proposed in combination with bipolar electrochemistry as a straightforward concept in analytical chemistry (Scheme 1).[19]



Scheme 1. Schematic illustration of the bipolar electrochemical actuation of polypyrrole cantilever. The feeder electrodes are graphite rods.

To achieve bipolar electrochemical processes endowed with enantioselectivity, chiral imprinted mesoporous platinum was combined with polypyrrole in a hybrid film, allowing the preferential reaction of one enantiomer, detected by a differential electromechanical deformation of the polypyrrole used as a freestanding actuator.[37] The relative difference of bending was used as a sign of enantioselectivity, but does not allow absolute discrimination of the two antipodes. In this context, a material, on which the enantiomers of a given chiral probe undergo electron transfer at two well-separated potentials when used as a bipolar electrode, could lead to a tool for absolute chiral recognition. As the above described oligomers reveal a thermodynamically different interaction with the two enantiomers of an analyte, combining them with polypyrrole as an actuator material should lead to an absolute electromechanical readout of chiral information. Such a yes/no answer, combined with a quantitative concentration measurement would greatly enhance the possible applications of this wireless approach. We report here the synthesis of a freestanding hybrid polymer film by electrodepositing an inherently chiral enantiopure monomer with a 3,3'-bibenzothiophene core (*i.e.* 2,2'-bis[2-(5,2'-bithienyl)]-3,3'-bithianaphthene, named BT_2T_4, **Scheme 2**) on polypyrrole (*i.e.* Ppy), which is electromechanically active, in order to combine chiral electrochemical recognition with an easy optical read out of the simultaneously occurring actuation. This proof-of-concept set-up is tested for the absolute discrimination of the two enantiomers of a chiral probe *i.e.* L- or D-DOPA.



Scheme 2. Chemical structures of the two enantiomers of the BT_2T_4 oligomers

EXPERIMENTAL SECTION

Synthesis of the polypyrrole film. For the synthesis of polypyrrole a solution of pyrrole monomer (0.2 M) (Sigma Aldrich) was dissolved in Milli Q water with dodecylbenzene sulfonate (DBS) (0.25 M) (Sigma Aldrich). After complete dissolution of both components, two gold coated glass slides were positioned parallel in a beaker at a distance of 1.5 cm. The beaker was filled with 12 cm^3 of this solution and one gold coated glass 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 0.004 A was applied for 1.5 h for the polymerization of pyrrole. The charge consumed during polymerization is around 20 C. After polymerization, the polymer coated substrate was washed with water, dried and used for further oligomerization of chiral monomer *i.e.* 2,2'-bis[2-(5,2'-bithienyl)]-3,3'-bithianaphthene.

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 with the polypyrrole substrate acting as working electrode in a small beaker containing 5 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 located at 1.5 cm from the working electrode 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 0.002 A for 40 minutes. After deposition of the oligo-(3,3'dibenzothiophene)-polypyrrole hybrid films, they were peeled off from the gold electrode and then properly cut to be used as actuators for the bipolar chiral recognition experiments. The total length of the bipolar electrode is 1.1 cm, 3 mm of which correspond to the actuator part (polypyrrole). In order to maximize the current density on the actuator section, the oligo-BT_2T_4 covered end is 5 mm in width while the naked Ppy (actuator part) is 1 mm.

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 (0.005 M) dissolved in water and 0.2 M $LiClO_4$. The reference electrode was Ag/AgCl and a platinum grid the counter electrode. The working electrode was a hybrid electrode composed of an oligo-(*S*)-BT_2T_4 layer, deposited on a freestanding Ppy film. This film was carefully isolated on the backside with varnish and connected with a 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 chiral recognition. For bipolar chiral recognition, enantiopure (*R*)- or (*S*)-oligo-(3,3'-dibenzothiophene)-polypyrrole hybrid films (1.1 cm length) were fixed in the center of the bipolar cell. Two graphite feeder electrodes were positioned at the extremities of the cell (5 cm apart). 0.2 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. For concentration dependent experiments, 2, 5, 10 and 15 mM L-DOPA solutions were analyzed with a (*S*)-oligo-(3,3'-dibenzothiophene)-polypyrrole hybrid film. For experiments with L- and D-DOPA mixtures, solutions with the enantiomers in 3mM/6mM and

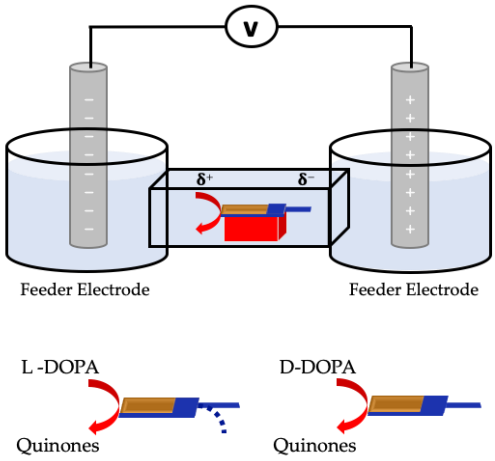
6mM/3mM L/D ratios were analyzed with a (*S*)-oligo-(3,3'-dibenzothiophene)-polypyrrole hybrid film.

The degree of actuation was recorded using a macroscope (LEICA Z16 APO) in video mode.

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

RESULTS AND DISCUSSION

The overall experimental set-up for absolute wireless chiral discrimination is illustrated in **Scheme 3**. The hybrid object, composed of enantiopure (*R*)- or (*S*)-oligomer BT_2T_4 (brown) electrodeposited onto Ppy (blue), is used as a bipolar electrode, immobilized on an inert support (red). It is mechanically very robust and stable, due to the strong interaction between the conducting oligomer and the polymer. Under the influence of the imposed electric field, the composite bipolar electrode is polarized with respect to the surrounding solution, leading to δ^+ and δ^- extremities. At the δ^+ side, electrooxidation of DOPA can occur, for which the enantiopure oligo-BT_2T_4 provides the chiral selectivity in terms of potential difference. At the δ^- extremity Ppy is reduced, accompanied by a deformation of the polymer.[37-40] In order to provide a sufficient amount of electrons for Ppy reduction, the bipolar electrode is designed in a way that the δ^+ extremity is about 5 times broader than δ^- extremity, analog to what has been reported previously.[41] The reduction of Ppy preferentially occurs, as demonstrated earlier,[38] on the rough side of the film, facing upwards in the present set-up. This is accompanied by an uptake of cations, inducing face selective swelling and thus significant bending.



Scheme 3. Schematic illustration of the bipolar cell used for wireless absolute discrimination of D- and L-DOPA. The dark brown part stands for the (*S*)-BT_2T_4 oligomer, whereas blue symbolizes the Ppy film. The dotted blue line represents the Ppy bending after enantioselective recognition. The distance between feeder electrodes is 5 cm and the length of the bipolar electrode is 1.1 cm.

Before performing chiral recognition experiments, it is necessary to control and characterize the modification of Ppy with oligo-BT_2T_4. Surface characterization of the polymer hybrid was performed using scanning electron microscopy (SEM). SEM images were recorded as a top view of three different regions of the bipolar electrode: *i)* at the junction between Ppy and oligo-BT_2T_4, *ii)* at the oligo-BT_2T_4 layer immobilized on top of Ppy, *iii)* at the pure Ppy layer. A clear difference in morphology is observed as shown in **Figure 1**. Oligo-BT_2T_4 shows a very bright and granular morphology related to the highly conducting surface, whereas the Ppy surface is darker and globular. The bottom side of the hybrid film is uniform, confirming the single side modification of the polypyrrole substrate. Both oligomer enantiomers show exactly the same surface morphology when they are deposited on Ppy, which is quite expected as they have the same oligomerization kinetics and contain the same amount of dopant.[42]

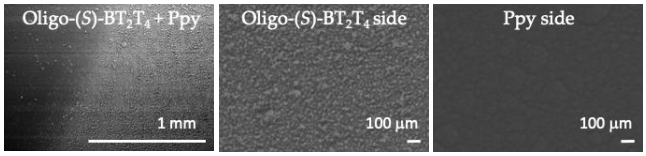


Figure 1. Top view SEM images of the freestanding hybrid film. A) Junction between the oligo-BT_2T_4 modified part (right) and the unmodified Ppy (left). B) The oligomer layer deposited on the Ppy support. C) the unmodified Ppy film.

Before proceeding to the electromechanical readout experiments, chiral recognition tests were performed by differential pulse voltammetry (DPV) using D-DOPA or L-DOPA, respectively, in aqueous $LiClO_4$ as supporting electrolyte. The enantioselectivity of the surface of oligo-(*S*)-BT_2T_4 with respect to D- or L-DOPA is depicted in **Figure 2**. From the DPV signal it is clear that the electrooxidative transformation of the two enantiomers occurs at significantly different potentials *i.e.* 0.5 V and 0.7 V vs. Ag|AgCl for L-and D-DOPA, respectively. This has already been demonstrated in previous studies[43] and constitutes the crucial ingredient for the absolute chiral discrimination in the follow-up bipolar experiments. It can be clearly seen that at ~0.45 V vs. Ag|AgCl only one of the two enantiomers is electrochemically oxidized. Therefore, it should be possible to transform exclusively L-DOPA at a bipolar electrode if the polarization potential difference between its two extremities is tuned at a value that is just enough to allow the oxidation of L-DOPA on one end together with Ppy reduction at the other end. Taking into account that Ppy reduction occurs at about –0.25 V vs. Ag|AgCl,[19] we can conclude that the threshold of such a polarization potential difference should be around 0.65 V.

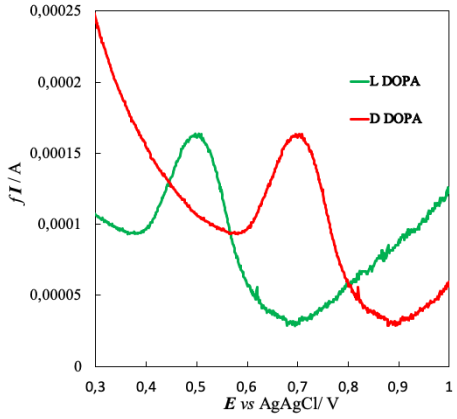


Figure 2. Differential pulse voltammetry in 0.2M $LiClO_4$ for the enantioselective electrooxidation of L- and D-DOPA (0.005M) on the surface at an oligo-(*S*)-BT_2T_4 surface, deposited on a freestanding Ppy film.

In order to confirm this value, bipolar electrochemistry was performed by using a hybrid film with oligo-(*S*)-BT_2T_4 or oligo-(*R*)-BT_2T_4 electrodeposited on Ppy. The potential difference between the feeder electrodes was slowly increased until a first sign of polymer bending could be observed. It was found that the minimum electric field required for selective recognition is 0.6 V/cm. For higher electric fields, both enantiomers can be electrooxidized. It still leads to a certain discrimination, as the rates of bending are different, but prevents from achieving the initial goal, that means absolute recognition of the two enantiomers by a wireless readout approach. When an electric field of 0.6 V/cm is applied to the Ppy-based bipolar electrode, modified with one or the other oligo-enantiomer, oligo-(*R*)-BT_2T_4/Ppy selectively recognizes D-DOPA, which results in a strong actuation of Ppy at its negatively polarized extremity, whereas absolutely no deflection is observed when L-DOPA is in the solution. The opposite effect was observed for oligo-(*S*)-BT_2T_4, which is able to recognize L-DOPA, inducing a deflection of Ppy, but remaining electromechanically inactive in the presence of D-DOPA. The difference between the initial (green) and final (red) bending state of the δ^- extremity of Ppy was used as an output signal during chiral recognition at a fixed time (40 s) as shown in **Figure 3** (see also video V1). The total deflection (= distance between the initial and final position of the pyrrole extremity) in the case of the appropriate enantiomer is about 1 mm, and this kind of deflection is sufficient to classify the device as an optical yes/no reader of chiral information.

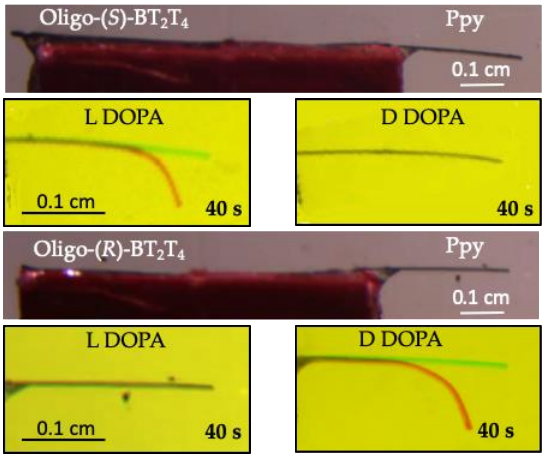


Figure 3. Bipolar enantioselective electrooxidation in 0.2 M $LiClO_4$ of L- and D-DOPA (5 mM) on the surface of oligo-(*S*)-BT_2T_4 and oligo-(*R*)-BT_2T_4 deposited on Ppy. Initial state (green) and final state (red) of the Ppy extremity during electromechanical deformation. Length of the bipolar electrode is 1.1cm. The electric field is 0.6 V/cm for all experiments. The readout time for all experiments is 40 sec.

Besides this first demonstration of absolute chiral discrimination via an on/off response, we wanted to check in the next step whether the approach can be also adapted to a more quantitative determination of chiral molecules. We therefore measured the degree of deflection as a function of analyte concentration. Four concentrations of L-DOPA (2, 5, 10 and 15 mM) were analysed with an oligo-(*S*)-BT_2T_4/Ppy bipolar electrode. The degree of deflection was found to be linear for this concentration range as shown in the calibration curve of **Figure 4**.

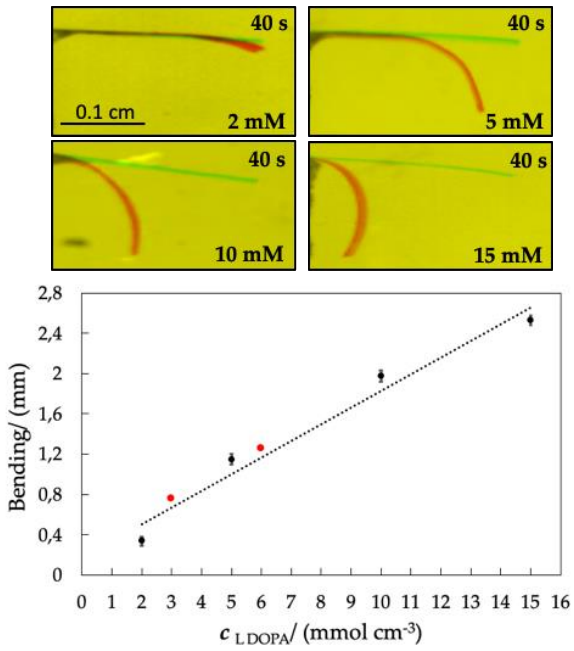


Figure 4. Concentration dependent deflection of Ppy for the enantioselective recognition of L-DOPA on oligo-(*S*)-BT_2T_4/Ppy and corresponding calibration curve. The readout time for each concentration is 40 sec. Length of the bipolar electrode is 1.1 cm. The electric field is 0.6 V/cm in all experiments. Errors bars correspond to three repetitions. Red dots refer to Ppy deflection for chiral recognition of L-DOPA (3mM, 6mM, respectively) in the simultaneous presence of D-DOPA (6mM, 3mM, respectively).

After testing the enantioselective deflection as a function of concentration, we have studied this hybrid actuator for the determination of the quantity of only one of the two enantiomers of DOPA (independently from the other) when they coexist, in different ratios, in the same solution. We report an example in **Figure 5**.

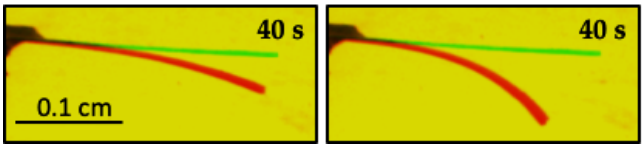


Figure 5. Enantioselective deflection of Ppy for two different solutions containing different ratios of L/D DOPA (3mM/ 6mM left, 6mM/ 3mM right). Oligo-(*S*)-BT_2T_4 was deposited on Ppy. The readout time for each concentration is 40 sec. Length of the bipolar electrode is 1.1 cm. The electric field is 0.6 V/cm in all the experiments.

The deflection of Ppy varies as a function of the ratio between the two enantiomers of DOPA. When oligo-(*S*)-BT_2T_4 is deposited on Ppy, the resulting bending is more pronounced in the presence of L-DOPA, the favorable enantiomer configuration for selective recognition. The bending response of the hybrid actuator in the presence of the L/D DOPA mixture is coherent with the concentration ratio used during the experiments (red dots in **Figure 4**: 0.7 mm vs. 1.3 mm deflection) and fits the calibration plot. This means that with these experiments it is possible to estimate selectively the concentration of only one of the two enantiomers of DOPA present in the mixed solution, the one that is easier to oxidize.

Moreover, the enantiomeric excess in mixed solutions of these two enantiomers could be indirectly determined if results from bipolar experiments are combined with another experiment where the total concentration of L- + D-DOPA is correlated to another analytical signal (for example current intensities of the chiral analyte recorded in a voltammetry experiment with an achiral electrode substrate like glassy carbon).[44] In this way it could be possible to estimate the total concentration of L- + D-DOPA in solution from a peak current vs. concentration calibration plot, while from the bipolar experiments the concentration of one of the two enantiomers (the one that oxidizes first) could be estimated. The enantiomeric excess could then be calculated by combining the two data.

CONCLUSION

Absolute enantiomeric discrimination has been successfully achieved for the first time with a wireless electromechanical readout concept based on the use of bipolar electrochemistry. A hybrid Ppy film, modified with oligomers bearing intrinsic chiral features, was used as a bipolar electrode. The chronopotentiometric surface modification of Ppy with enantiopure oligo-BT_2T_4 can be optimized by adjusting the experimental conditions (*e.g.* type of supporting electrolyte, monomer concentration). The morphology of the hybrid film proves to be overall robust and mechanically strong enough to be handled as a free-standing film during the bipolar electrochemistry experiments. Actuation efficiency can be controlled by the applied electric field, allowing addressing selectively only one of the two enantiomers of DOPA as a chiral model analyte. The degree of actuation is found to be directly proportional to the analyte concentration, using both the single enantiomer and mixtures of the two enantiomers. This enables the selective measurement of enantiomers of chiral probes, both, from a qualitative and quantitative point of view and, as a consequence, the determination of the enantiomeric excess. Further optimization and generalization will open up interesting perspectives for using this approach as an alternative and straightforward tool to analyze samples containing chiral molecules.

ASSOCIATED CONTENT

Supporting Information

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

V1 Bipolar enantioselective oxidation (.mp4)

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Author Contributions

S.A. and B.G. designed and performed 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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